07/252645 9200/3306

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: RICHARD L. DUNN et al. Docket: 8905.70USPA
Patent No.: 4,938,763
Issued: July 3, 1990
Title: BIODEGRADABLE IN-SITU FORMING IMPLANTS AND METHODS OF PRODUCING THE SAME

CERTIFICATE UNDER 37 CFR 1.10
'Express Mail' mailing label number: EM402707866US
Date of Deposit: October 23, 1998
I hereby certify that this paper or fee is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner of Patents and Trademarks, Washington, D.C. 20231.

By: Pat Zastrow
Name: Pat Zastrow

BOX PATENT EXT
Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

- ☒ Transmittal Sheet in duplicate containing Certificate of Mailing
- ☒ Check(s) in the amount of $1,120.00, for APPLICATION FOR EXTENSION OF PATENT TERM
- ☒ Other: APPLICATION FOR EXTENSION OF PATENT TERM UNDER 35 U.S.C. §156 AND EXHIBITS, WITH CERTIFIED DUPLICATE OF SAME, AND THREE WORKING COPIES
- ☒ Return postcard

Please consider this a PETITION FOR EXTENSION OF TIME for a sufficient number of months to enter these papers, if appropriate. Please charge any additional fees or credit overpayment to Deposit Account No. 13-2725. A duplicate of this sheet is enclosed.

MERCHANT, GOULD, SMITH, EDELL,
WELTER & SCHMIDT
3100 Norwest Center, Minneapolis, MN 55402
(612) 332-5300

By: Ronald A. Daignault
Name: Ronald A. Daignault
Reg. No.: 25,968
RAD:kf

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Name: Ronald A. Daignault
Reg. No.: 25,968
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PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

U.S. Patent No.:	4,938,763	Docket No.:	8905.70USPA
Patentee:	RICHARD L. DUNN, et al.		
Issue Date:	July 3, 1990		
Title:	BIODEGRADABLE IN-SITU FORMING IMPLANTS AND METHODS OF PRODUCING THE SAME		

APPLICATION FOR EXTENSION OF
PATENT TERM UNDER 35 U.S.C. §156

BOX PATENT EXT.
Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

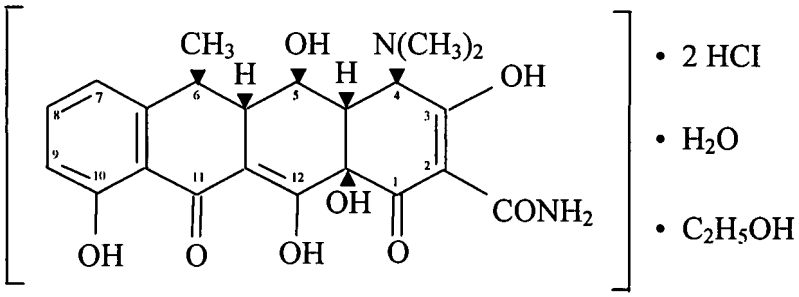
Pursuant to §201(a) of the Drug Price Competition and Patent Term Restoration Act of 1984, 35 U.S.C. §156, Atrix Laboratories, Inc., of 2579 Midpoint Drive, Fort Collins, Colorado, 80525, the assignee of record, hereby requests an extension of the patent term of United Sates Patent No. 4,938,763.

The following information is submitted in accordance with 35 U.S.C. §156(d) and 35 C.F.R. §1.740, and follows the numerical format set forth in 37 C.F.R. §1.740.

(1) A complete identification of the approved product as by appropriate chemical and generic name, physical structure or characteristics:

The approved product is ATRIDOX™. The ATRIDOX™ product is a subgingival controlled-release product composed of a two syringe mixing system. Syringe A contains 450 mg of an Atrigel® Delivery System which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) dissolved in 63.3% N-methyl-2-pyrrolidone. Syringe B contains doxycycline hyclate which is equivalent to 42.5 mg doxycycline, a broad-spectrum antibiotic. Upon mixing of the doxycycline powder with the flowable polymeric formulation, the constituted product is a pale yellow to yellow viscous liquid with a concentration of 10% doxycycline hyclate. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days.

Chemically, the active ingredient in ATRIDOX™ is doxycycline hyclate, USP. This active ingredient has the following structural formula:



ATRIDOX™ is a pharmaceutical for periodontal use in the treatment of chronic adult periodontitis; see the section entitled **Description** Exhibit 1 **(PACKAGE INSERT)** which is the product information sheet for the approved product.

(2) A complete identification of the Federal statute including the applicable provision of law under which the regulatory review occurred:

The regulatory review occurred under §505(b) of the Federal Food, Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. §301 et seq. Section 505 provides for the submission and approval of new drug applications ("NDAs") for products.

(3) An identification of the date on which the product received permission for commercial marketing or use under the provision of law under which the applicable regulatory review period occurred:

ATRIDOX™ was approved by the Food & Drug Administration ("FDA") for commercial marketing pursuant to §505(b) of the FFDCA on September 3, 1998; see Exhibit 2 **(APPROVAL LETTER)**.

(4) In the case of a human drug product, an identification of each active ingredient in the product and as to each active ingredient, a statement that it has not been previously approved for commercial marketing or use under the Federal Food, Drug and

Cosmetic Act, the Public Health Service Act, or the Virus–Serum–Toxin Act, or a statement of when the active ingredient was approved for commercial marketing or use (either alone or in combination with other active ingredients), the use for which it was approved, and the provision of law under which it was approved.

The active ingredients in ATRIDOX™ are doxycycline hyclate and polymeric formulation delivery system. Each of these individual agents has been approved previously. Doxycycline hyclate is a broad spectrum antibiotic initially approved in 1957; see DOXYCYCLINE HYCLATE USP, XXII, 1990, pages 479–480. The poly(DL–lactide) and N–methyl–2–pyrrolidone ingredients, in combination, in a slightly different formulation from the present product were approved as a medical device on March 21, 1996 (reference 510(k) No. K 955838). ATRIDOX™ is a two syringe mixing system containing a fixed dosage in one syringe of the delivery system containing the poly(DL–lactide), 36.7% in 63.3% N–methyl–2–pyrrolidone, and in a second syringe a fixed dosage of doxycycline hyclate, equivalent to 42.5 mg doxycycline. The dosage combination of these ingredients in ATRIDOX™ has not been previously approved.

(5) A statement that the application is being submitted within the sixty day period permitted for submission pursuant to §1.720(f) and an identification of the date of the last day on which the application could be submitted.

The product was approved for commercial marketing on September 3, 1998, and the last day within the sixty day period permitted for submission of an application for extension of the patent is November 3, 1998. The date of submission of the present application is no later than November 3, 1998, and therefore, the present application has been timely filed.

(6) A complete identification of the patent for which an extension is being sought by the name of the inventor, the patent number, the date of issue, and the date of expiration:

U.S. PATENT NUMBER: 4,938,763
INVENTOR: Richard L. Dunn, et al.

ISSUE DATE: July 3, 1990
EXPIRATION DATE: October 3, 2008

(7) A copy of the patent for which an extension is being sought including the entire specification (including claims) and drawings:

A copy of U.S. Patent No. 4,938,763 is attached as Exhibit 3 (**PATENT**).

(8) A copy of any disclaimer, certificate of correction, receipt of maintenance fee payment, or reexamination certificate issued in the patent:

No disclaimer or certificate of correction has been issued. A reexamination certificate was issued on July 4, 1995. A copy of the reexamination certificate is attached as Exhibit 4A. A copy of the receipt showing the first maintenance fee payment is attached as Exhibit 4B.

(9) A statement that the patent claims the approved product or a method of using or manufacturing the approved product, and a showing which lists each applicable patent claim and demonstrates the manner in which each applicable patent claim reads on the approved product or a method of using or manufacturing the approved product:

The patent claims the method of making the approved product ATRIDOX™ in claims 1–7 and 13–18.

Claims 1, 3, 5–7 and 13–18 are set forth below, including the amended claims by reexamination as noted:

Claim 1.

A method of forming [an] *a biodegradable* implant in–situ, in a living body, comprising the steps of:

(a) dissolving a non–reactive, [water–insoluble] *thermoplastic* polymer *that is water–insoluble and is biodegradable by simple or enzymatically catalyzed hydrolysis,* in a biocompatible, water–soluble solvent to form a liquid;

(b) placing said liquid within said body; and

(c) allowing said [solvent to dissipate to produce a] *liquid to contact body fluid to dissipate or diffuse the solvent into the body fluid and cause the thermoplastic polymer to coagulate or solidify to produce the biodegradable* solid implant.

Claim 3.

The method of claim 1, and further comprising delivering said liquid in–situ through a needle.

Claim 5.

The method of claim 1, and further comprising the step of adding an effective amount of biologically active agent to said liquid to provide an implant which releases said agent by diffusion, erosion or a combination of diffusion and erosion as said [plant biodegrade] *implant biodegrades*.

Claim 6.

The method of claim 5, wherein said implant is formed in a periodontal pocket in said body.

Claim 7.

The method of claim 6, wherein said biologically–active agent is selected from the group consisting of benzophenanthridine alkaloid and tetracycline.

Claim 13.

A biodegradable drug delivery implant for a body produced according to the method of claim 5.

Claim 14.

The method of claim 1, wherein said polymer is biodegradable.

Claim 15.

The method of claim 1, wherein said polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polydioxanones, polycarbonates, polyhydroxybutyrates, polyalkylene oxalates, polyanhydrides, polyamides, polyesteramides, polyurethanes, polyacetals, polyketals, polyorthocarbonates, polyphosphazenes, polyhydroxyvalerates, polyalkylene succinates, poly(malic acid), poly(amino acids), chitin, chitosan, and polyorthoesters, and copolymers, terpolymers and combination sand mixtures thereof.

Claim 16.

The method of claim 1, wherein said polymer is selected from the group consisting of polylactides, polycaprolactones and copolymers thereof with glycolide.

Claim 17.

The method of claim 1, wherein said solvent is selected from the group consisting of N–methyl–2–pyrrolidone, 2–pyrrolidone, ethanol, propylene glycol, acetone, ethyl acetate, methyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid and l–dodecylazacycloheptan–2–one and combinations and mixtures thereof.

Claim 18.

The method of claim 1, wherein said solvent is selected from the group consisting of N–methyl–2–pyrrolidone, 2–pyrrolidone, dimethyl sulfoxide and acetone, and a combination or mixture thereof.

Regarding Claim 7

Claim 7 is a dependent claim which covers the process for making the ATRIDOX™ product when considering the claims that this dependent claim depends upon. Thus if written in independent form with the limitations of the claims dependent thereon, claim 7 covers the approved ATRIDOX™ product. For example, claim 7 requires the biologically–active agent to be "selected from the group consisting of . . . tetracycline." Doxycycline is a broad–spectrum semi–synthetic tetracycline.

Claim 7 dependent on claim 6 requires that the implant containing doxycycline is formed "in a periodontal pocket in said body."

Both claims 7 and 6 depend on claim 5 which requires the step of "adding an effective amount of biologically active agent to said liquid", in this case doxycycline (claim 7), "to provide an implant which releases said agent by diffusion, erosion or a combination of diffusion and erosion as said implant biodegrades." The liquid is the polymer liquid for which process is covered in claims 1–4.

Claims 1–4 are directed to the preparation of the polymer liquid component delivered through a needle (claim 3) and where a lactide polymer may be used (claim 4).

Regarding Claims 15–18

These claims further identify the polymer component as requiring a polylactide and N–methyl–2–pyrrolidone as solvent. See claims 15–18. The polylactide in N–methyl–2–pyrrolidone is part of the ATRIDOX™ product as the polymer liquid which is mixed with doxycycline (claim 7) using a two syringe mixing system.

(10) A statement beginning on a new page, of the relevant dates and information pursuant to 35 U.S.C. §156(g) in order to enable the Secretary of Health and Human Services or the Secretary of Agriculture, as appropriate, to determine the applicable regulatory review period as follows:

(i) For a patent claiming a human drug, antibiotic, or human biological product, the effective date of the investigational new drug (IND) application and the IND number; the date on which a new drug application (NDA) or a Product License Application (PLA) was initially submitted and the NDA or PLA number and the date on which the NDA was approved for the Product License issued;

On April 17, 1990, Atrix Laboratories, Inc. submitted to the food and Drug Administration a "Notice of Claimed Investigational Exemption for a New Drug" (IND) for the ATRIDOX™ product. A copy of this letter is submitted herewith as Exhibit 5 (**IND SUBMISSION LETTER**).

The IND was assigned number 34,690. It was received by the FDA on April 18, 1990. The IND became effective on May 18, 1990, which is thirty days after receipt of the IND by the FDA; see Exhibit 6 (**IND ACKNOWLEDGMENT LETTER**) attached hereto. This establishes the beginning of the "regulatory review period" under 35 U.S.C. §156(g)(1) as May 18, 1990.

On July 15, 1991, Atrix Laboratories, Inc. requested that the IND be placed into inactive status by the F.D.A. A copy of the letter to the F.D.A. is attached as Exhibit 7. The F.D.A. acknowledged Atrix's request and indicated by a letter of November 5, 1991 that the IND application had now been placed on inactive status. A copy of the F.D.A. letter is attached as Exhibit 8. Atrix Laboratories, Inc. reactivated the IND for the ATRIDOX™ product by submission of clinical protocol ACS–28 on June 29, 1992. A copy of the cover letter is attached as Exhibit 9. Accordingly, the "regulatory review" became effective again thirty days following this submission, July 29, 1992, leaving a period of inactivity of 266 days.

On March 31, 1997, a new drug application was submitted under §505(b) of the Federal Food, Drug, and Cosmetic Act (FFDCA) and §314.50 of Title 21 Code of Federal Regulations for ATRIDOX™ by Atrix Laboratories, Inc. A copy of the cover letter attached to the NDA of March 31, 1997 is submitted herewith as Exhibit 10 (**NDA SUBMISSION LETTER**).

The F.D.A. acknowledged receipt of the NDA submission on April 1, 1997 and assigned the NDA No. 50–751. The letter also indicated that the actual application was given its application date of April 7, 1997 when the user fee payment was received. A copy of the F.D.A. letter is attached as Exhibit 11.

The NDA was approved on September 3, 1998. See Exhibit 2.

Thus, for the purposes of determining the "regulatory review period" under 35 U.S.C. §156(g)(1) the date of the first approval of ATRIDOX™ is September 3, 1998.

(11) A brief description, beginning on a new page, of the significant activities undertaken by the marketing applicant during the applicable regulatory review period with respect to the approved product and the significant dates applicable to such activities:

As described above in item (10), the IND for ATRIDOX™ became effective on May 18, 1990. Following an inactive period of 266 days, the IND was reactivated effective July 29, 1992. The correspondence between Atrix Laboratories, Inc. and the F.D.A. are summarized in the attached Exhibit 12 (**CORRESPONDENCE INDEX IND 34, 690**). The clinical studies used to support NDA 50-651 submitted by Atrix Laboratories, Inc. included ACS-32, ACS-38, AGD-9607, AGD-9701, AGD-9705, ACS-28, ACS-33, ACS-34, ACS-35, and AGD-9603. A copy of the clinical investigation plan summarized in the last IND annual report (1994) is attached as Exhibit 13.

Subsequent to the submission of the NDA, Atrix Laboratories, Inc. had numerous contacts and meetings with the F.D.A. with respect to the application and these are summarized in the attached Exhibit 14 (**PROJECT 1010 CORRESPONDENCE INDEX**).

(12) A statement, beginning on a new page, that in the opinion of the applicant the patent is eligible for the extension and a statement as to the length of the extension claimed, including how the length of extension was determined:

Statement of Eligibility of the Patent for Extension
Under 35 U.S.C. §156(a) and (c)(4)

Section 156(a) provides, in relevant part, that the term of a patent which claims a product, a method of using a product, or a method of manufacturing a product shall be extended if (1) the term of the patent has not expired before an application for extension is submitted, (2) the term of the patent has never been extended, (3) the application for extension is submitted by the owner of record of the patent or its agent in accordance with 35 U.S.C. §156(d), (4) the product has been subject to a regulatory review period before its commercial marketing or use, and (5) the permission for the commercial marketing or use of the product after such regulatory review period is the first permitted commercial marketing or use of the product under the provision of law under which such regulatory review period occurred; and §156(c)(4) provides, that in no event shall more than one patent be extended for the same regulatory review period for any product.

As described by corresponding number, each of these elements is satisfied here:

(1) The statutory term of U.S. Patent No. 4,938,763 expires on October 3, 2008. This application has, therefore, been submitted before the expiration of the patent term. All required maintenance fees have been paid.

(2) The term of this patent has never been extended.

(3) This application is submitted by Atrix Laboratories, Inc., the owner of record of Patent No. 4,938,763, by assignment recorded at Reel 6056, frame 0945. This application is submitted in accordance with 35 U.S.C. §156(d) in that it is submitted within the sixty–day period beginning on the date, September 3, 1998, that the product received permission for marketing under the Federal Food, Drug and Cosmetic Act and contains the information required under 35 U.S.C. §156(d).

(4) As evidenced by the September 3, 1998 letter from the FDA, Exhibit 2 (**APPROVAL LETTER**), the product was subject to a regulatory review period under §505(b) of the FFDCA before its commercial marketing or use.

(5) The permission for the commercial marketing of ATRIDOX™ after regulatory review under §505(b) is the first permitted commercial marketing of the approved product. This

is confirmed by the absence of any approved new drug application under which ATRIDOX™ could be commercially marketed prior to September 3, 1998.

Statement as to Length of Extension Claimed

in Accordance with 37 C.F.R. §1.775

The term of U.S. Patent No. 4,938,763 should be extended for a period of 1,431 days to September 3, 2012.

The period of extension is determined in accordance with 35 U.S.C. §156 and follows the format set forth in 37 CFR §1.775(c) and (d).

37 CFR §1.775(c) The length of the regulatory review period for a human drug, antibiotic drug or human biological product will be determined by the Secretary of Health and Human Services. Under 35 U.S.C. §156(g)(1)(B), it is the sum of —

(1) The number of days in the period beginning on the date an exemption under subsection (i) of section 505 or subsection (d) of section 507 of the Federal Food, Drug, and Cosmetic Act became effective for the approved product and ending on the date the application was initially submitted for such product under those sections or under section 351 of the public Health Service Act;

The number of days between the effective date of the IND, May 18, 1990, and the initial submission of the NDA, April 7, 1997, is a period of 2,515 days

and

(2) The number of days in the period beginning on the date the application was initially submitted for the approved product under section 351 of the Public Health Service Act, subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act and ending on the date such application was approved under such section.

The number of days between the effective submission of the NDA, April 7, 1997, to NDA approval, September 3, 1998, is a period of 490 days.

37 C.F.R. §1.775(d) The term of the patent as extended for a human drug, antibiotic drug or human biological product will be determined by —

(1) Subtracting from the number of days determined by the Secretary of Health and Human Services to be in the regulatory review period:

(i) The number of days in the periods of paragraphs (c)(1) an d(c)(2)of this section which were on and before the date on which the patent issued;

The number of days in the period of the IND, effective on May 18, 1990, which were on or before July 3, 1990, the date the patent was issued, is a period of 45 days,

2,515 days minus 45 days equals 2,470 days, and

the number of days in the period of the NDA, initial submission effective date of April 7, 1997, which were on or before July 3, 1990, the date the patent was issued, is a period of 0 days,

490 days minus 0 days equals 490 days.

(ii) The number of days in the periods of paragraphs (c)(1) and (c)(2) of this section during which it is determined under 35 U.S.C. §156(D)(2)(b) by the Secretary of Health and Human Services that applicant did not act with due diligence;

The number of days the applicant did not act with due diligence is 266 days,

therefore,

2,470 days minus 266 days equals 2,204 days.

490 days minus 0 days equals 490 days.

(iii) One–half the number of days remaining in the period defined by paragraph (c)(1) of this section after that period is reduced in accordance with paragraphs (d)(1)(i) and (ii) of this section; half days will be ignored for purposes of subtraction;

One–half of 2,204 days equals 1,102 days.

Thus, U.S. Patent No. 4,938,763 should be entitled to an extension of 1,592 days (1,102 days plus 490 days).

(2) By adding the number of days determined in paragraph (d)(1) of this section to the original term of the patent as shortened by any terminal disclaimer;

Adding 1,592 days to October 3, 2008, the original term of the patent (no terminal disclaimer was made), extends the term to February 12, 2013.

(3) By adding 14 years to the date of approval of the application under section 351 of the Public Health Service Act, or subsection (b) of section 505 or section 507 of the Federal Food, Drug, and Cosmetic Act;

Adding 14 years to September 3, 1998, which is the date of approval of the application, gives the date of September 3, 2012.

(4) By comparing the dates for the ends of the periods obtained pursuant to paragraphs (d)(2) and (d)(3) of this section with each other and selecting the earlier date;

The earlier date is September 3, 2012.

(5) If the original patent was issued after September 24, 1984,

(i) By adding 5 years to the original expiration date of the patent or any earlier date set by terminal disclaimer;

Adding 5 years to the original expiration date of the patent (October 3, 2008) gives the date of October 3, 2013.

and

(ii) By comparing the dates obtained pursuant to paragraphs (d)(4) and (d)(5)(i) of this section with each other and selecting the earlier date:

Comparing October 3, 2013 and September 3, 2012, the earlier date is September 3, 2012, and the patent term should therefore be extended to September 3, 2012.

(6) If the original patent was issued before September 24, 1984,

This is not applicable for the patent.

(13) Applicant acknowledges a duty to disclose to the Commissioner of Patents and Trademarks and to the Secretary of Health and Human Services any information which is material to any determination to be made relative to the application for extension.

Applicant is unaware of any additional information material to this application for extension.

(14) Prescribed Fee:

The prescribed fee of $1,120.00 for receiving and acting on this application for extension of patent term is attached. Please charge any deficiencies in the amount of the fee above or credit any overpayment to Deposit Account No. 13–2725.

(15) The name, address and telephone number of the person to whom inquiries and correspondence relating to the application for patent term extension are to be directed:

Ronald A. Daignault
Reg. No. 25,968
Merchant, Gould, Smith, Edell,
Welter & Schmidt, P.A.
3100 Norwest Center
90 South Seventh Street
Minneapolis, MN 55402-4131
Telephone: (612) 371-5381
Fax: (612) 332-9081

(16) A duplicate of the application papers, certified as such.

A duplicate of the application papers, certified as such, is submitted herewith.

(17) An oath or Declaration as set forth in paragraph (b) of 37 C.F.R. §1.740.

DECLARATION

The undersigned is authorized on behalf of Atrix Laboratories, Inc., the owner of record of U.S. Patent No. 4,938,763, to apply for an extension of the term of this patent. I declare that: I have reviewed and understand the contents of this Application being submitted pursuant to 35 U.S.C. §156; that I believe that the patent is subject to extension pursuant to 37 C.F.R. §1.710; that I believe that the length of extension claimed is fully justified under 35 U.S.C. §156 and the applicable regulations; and that I believe that the patent for which this extension is being sought meets the conditions for extension of the term of a patent as set forth in 37 C.F.R. §1.720.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application and any extension of U.S. Patent No. 4,938,763.

Respectfully submitted,
ATRIX LABORATORIES, INC.
By their Attorney,

October 23, 1998
Date

Ronald A. Daignault
Reg. No. 25,968
Merchant, Gould, Smith, Edell,
Welter & Schmidt, P.A.
3100 Norwest Center
Minneapolis, MN 55402-4131
(612) 371-5381

LIST OF EXHIBITS

Exhibit 1

(PACKAGE INSERT)

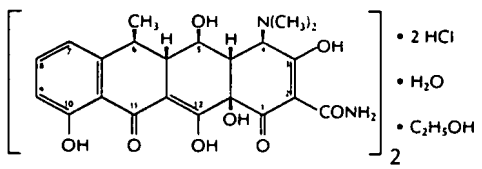
DESCRIPTION

The ATRIDOX™ product* is a subgingival controlled-release product composed of a two syringe mixing system. Syringe A contains 450 mg of the ATRIGEL® Delivery System, which is a bioabsorbable, flowable polymeric formulation composed of 36.7% poly(DL-lactide) (PLA) dissolved in 63.3% *N*-methyl-2-pyrrolidone (NMP). Syringe B contains doxycycline hyclate which is equivalent to 42.5 mg doxycycline. The constituted product is a pale yellow to yellow viscous liquid with a concentration of 10% of doxycycline hyclate. Upon contact with the crevicular fluid, the liquid product solidifies and then allows for controlled release of drug for a period of 7 days.

*ATRIDOX is a trademark of Block Drug Corporation. ATRIGEL is a registered trademark of Atrix Laboratories, Inc.

Doxycycline is a broad-spectrum antibiotic synthetically derived from oxytetracycline.

The structural formula of doxycycline hyclate is:



Empirical Formula: $(C_{22}H_{24}N_2O_8 \cdot HCl)_2 \cdot C_2H_6O \cdot H_2O$

CLINICAL PHARMACOLOGY

Microbiology

Doxycycline is a broad-spectrum semisynthetic tetracycline.[1] Doxycycline is bacteriostatic, inhibiting bacterial protein synthesis due to disruption of transfer RNA and messenger RNA at ribosomal sites.[1] In vitro testing has shown that *Porphyromonas gingivalis, Prevotella intermedia, Campylobacter rectus,* and *Fusobacterium nucleatum,* which are associated with periodontal disease, are susceptible to doxycycline at concentrations ≤ 6.0 µg/mL.[2] A single-center, single-blind, randomized, clinical study in 45 subjects with periodontal disease demonstrated that a single treatment with ATRIDOX™ resulted in the reduction in the numbers of *P. gingivalis, P. intermedia, C. rectus, F. nucleatum, Bacteroides forsythus,* and *E. corrodens* in subgingival plaque samples. Levels of aerobic and anaerobic bacteria were also reduced after treatment with ATRIDOX™. The clinical significance of these findings, however, is not known. During these studies, no overgrowth of opportunistic organisms such as Gram-negative bacilli and yeast were observed. However, as with other antibiotic preparations, ATRIDOX™ therapy may result in the overgrowth of nonsusceptible organisms including fungi. (See **PRECAUTIONS**)

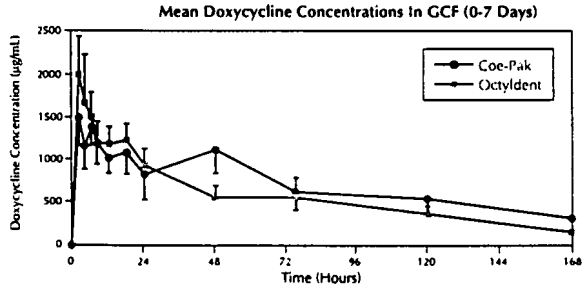
Pharmacokinetics

In a clinical pharmacokinetic study, subjects were randomized to receive either ATRIDOX™ covered with Coe-Pak™ periodontal dressing (n=13), ATRIDOX™ covered with Octyldent™ periodontal adhesive (n=13), or oral doxycycline (n=5) (according to package dosing instructions). The doxycycline release characteristics in gingival crevicular fluid (GCF), saliva, and serum were evaluated.

Doxycycline levels in GCF peaked (~1,500 µg/mL and ~2000 µg/mL for Coe-Pak™ and Octyldent™ groups, respectively) 2 hours following treatment with ATRIDOX™. These levels remained above 1000 µg/mL through 18 hours, at which time the levels began to decline gradually. However, local levels of doxycycline remained well above the minimum inhibitory concentration (MIC_{90}) for periodontal pathogens (≤ 6.0 µg/mL)[2] through Day 7. In contrast, subjects receiving oral doxycycline had peak GCF levels of ~2.5 µg/mL at 12 hours following the initial oral dosing with levels declining to ~0.2 µg/mL by Day 7. High variability was observed for doxycycline levels in GCF for both oral and ATRIDOX™ treatment groups.

The ATRIDOX™ doxycycline release profile in GCF is illustrated in the figure below.

Mean Doxycycline Concentrations in GCF (0-7 Days)



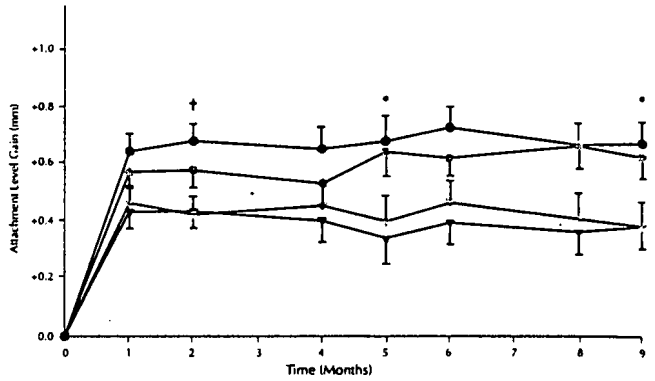
The maximum concentration of doxycycline in saliva was achieved at 2 hours after both treatments with ATRIDOX™, with means of 4.05 µg/mL and 8.78 µg/mL and decreased to 0.36 µg/mL and 0.23 µg/mL at Day 7 for the Coe-Pak™ group and the Octyldent™ group, respectively.

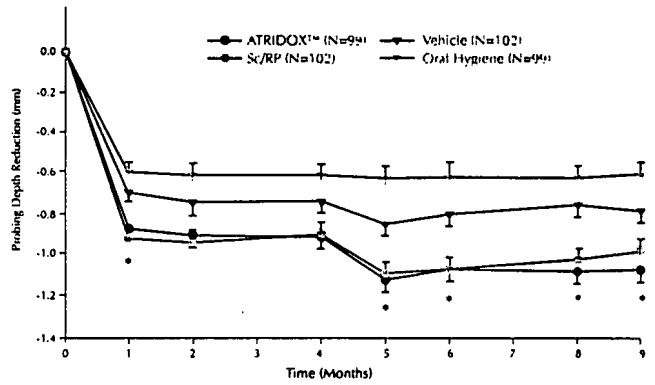
The concentration of doxycycline in serum following treatment of ATRIDOX™ never exceeded 0.1 µg/mL.

CLINICAL STUDIES

In two well-controlled, multicenter, parallel-design, nine-month clinical trials, 831 patients patients (Study 1=411; Study 2=420) with chronic adult periodontitis characterized by a mean probing depth of 5.9 to 6.0 mm were enrolled. Subjects received one of four treatments: 1) ATRIDOX™, 2) Scaling and Root Planing, 3) Vehicle Control, or 4) Oral Hygiene. Treatment was administered to sites with probing depths 5 mm or greater that bled on probing. Subjects with detectable subgingival calculus on greater than 80% of all tooth surfaces were excluded from enrollment. All subjects received a second administration of the initially randomized treatment four months after their Baseline treatment. Changes in the efficacy parameters, attachment level, pocket depth, and bleeding on probing, between Baseline and Month 9 showed that: 1) ATRIDOX™ was superior to Vehicle Control and Oral Hygiene, and 2) ATRIDOX™ met the decision rule of being at least 75% as good as Scaling and Root Planing (SRP) (the standard of at least 75% as good as SRP is required for any product approved as a stand alone therapy for periodontitis). Clinicians should note that the studies were of nine months duration. Additional research would be necessary to establish long term comparability to SRP. The results of Studies #1 and 2 for efficacy parameters of attachment level gain and probing depth reduction are included in the following graphs.

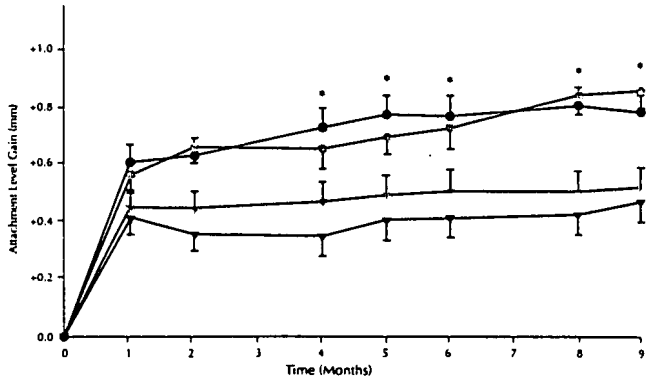
STUDY #1

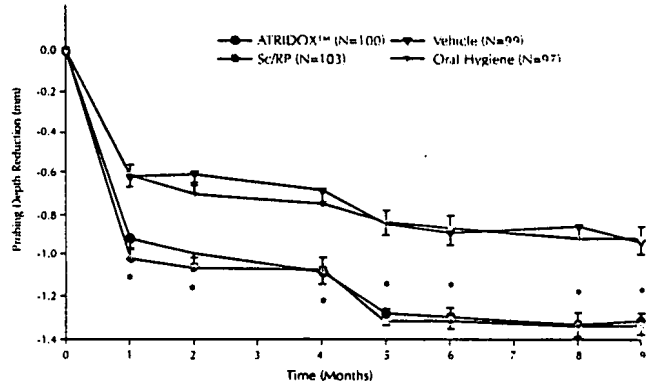




* denotes statistically significant superiority of ATRIDOX™ and Sc/RP vs. Vehicle and Oral Hygiene
† denotes statistically significant superiority of ATRIDOX™ vs. Vehicle and Oral Hygiene
Data were not collected at months 3 and 7

STUDY #2





* denotes statistically significant superiority of ATRIDOX™ and Sc/RP vs. Vehicle and Oral Hygiene
† denotes statistically significant superiority of ATRIDOX™ vs. Vehicle and Oral Hygiene
Data were not collected at months 3 and 7

A third clinical trial was conducted to determine whether the product can be left in the pocket to bioabsorb or be expelled naturally and achieve comparable clinical results. In this study the product was retained with Octyldent™ dental adhesive rather than Coe-Pak™ periodontal dressing as in the previously mentioned studies. This was a 3-arm, randomized, controlled, parallel group, single blind trial that enrolled 605 subjects. The patient population studied and study design were comparable to that in Studies 1 and 2. Subjects received one of three treatments: 1) ATRIDOX™ with Coe-Pak™ removed after 7 days as in the pivotal trials, 2) ATRIDOX™ retained with Octyldent™ and left to bioabsorb or be expelled naturally or 3) Vehicle Control with Octyldent™ left to bioabsorb or be expelled naturally. Changes in the efficacy parameters, attachment level, pocket depth and bleeding on probing were equivalent to those observed in Studies 1 and 2. The results of the third study support the use of ATRIDOX™ retained with Octyldent™ and left to bioabsorb or be expelled naturally.

INDICATIONS AND USAGE

ATRIDOX™ is indicated for use in the treatment of chronic adult periodontitis for a gain in clinical attachment, reduction in probing depth, and reduction in bleeding on probing.

CONTRAINDICATIONS

ATRIDOX™ should not be used in patients who are hypersensitive to doxycycline or any other drug in the tetracycline class.

WARNINGS

THE USE OF DRUGS OF THE TETRACYCLINE CLASS DURING TOOTH DEVELOPMENT (LAST HALF OF PREGNANCY, INFANCY, AND CHILDHOOD TO THE AGE OF EIGHT YEARS) MAY CAUSE PERMANENT DISCOLORATION OF THE TEETH. This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses. Enamel hypoplasia has also been reported. TETRACYCLINE DRUGS, THEREFORE, SHOULD NOT BE USED IN THIS AGE GROUP, OR IN PREGNANT WOMEN, UNLESS OTHER DRUGS ARE NOT LIKELY TO BE EFFECTIVE OR ARE CONTRAINDICATED. Results of animal studies indicate that tetracyclines cross the placenta, are found in fetal tissues, and can have toxic effects on the developing fetus (often related to skeletal development). Evidence of embryotoxicity has also been noted in animals treated early in pregnancy. If any tetracycline is used during pregnancy, the patient should be apprised of the potential hazard to the fetus.

Photosensitivity manifested by an exaggerated sunburn reaction has been observed in some individuals taking doxycycline or other tetracyclines. Patients apt to be exposed to direct sunlight or ultraviolet light should be advised that this reaction can occur with tetracycline drugs.

PRECAUTIONS

General:

ATRIDOX™ has not been clinically tested in pregnant women.

ATRIDOX™ has not been clinically evaluated in patients with conditions involving extremely severe periodontal defects with very little remaining periodontium.

ATRIDOX™ has not been clinically tested for use in the regeneration of alveolar bone, either in preparation for or in conjunction with the placement of endosseous (dental) implants or in the treatment of failing implants.

ATRIDOX™ has not been clinically tested in immunocompromised patients (such as patients immunocompromised by diabetes, chemotherapy, radiation therapy, or infection with HIV).

As with other antibiotic preparations, ATRIDOX™ therapy may result in overgrowth of nonsusceptible organisms, including fungi.[1] The effects of prolonged treatment, greater than six months, have not been studied.

ATRIDOX™ should be used with caution in patients with a history of or predisposition to oral candidiasis. The safety and effectiveness of ATRIDOX™ have not been established for the treatment of periodontitis in patients with coexistent oral candidiasis.

Information for Patients:

Mechanical oral hygiene procedures (i.e., tooth brushing, flossing) should be avoided on any treated areas for 7 days.

Avoid excessive sunlight or artificial ultraviolet light while receiving doxycycline.

Doxycycline may decrease the effectiveness of birth control pills.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Long-term studies in animals to evaluate carcinogenic potential of doxycycline have not been conducted. However, there has been evidence of oncogenic activity in rats in studies with the related antibiotics, oxytetracycline (adrenal and pituitary tumors), and minocycline (thyroid tumors). Likewise, although mutagenicity studies of doxycycline have not been conducted, positive results in in vitro mammalian cell assays have been reported for related antibiotics (tetracycline, oxytetracycline). Doxycycline administered orally at dosage levels as high as 250 mg/kg/day had no apparent effect on the fertility of female rats. Effect on male fertility has not been studied.

Pregnancy Category D. See "WARNINGS" section

Nursing Mothers:

Tetracyclines appear in breast milk following oral administration. It is not known whether doxycycline is excreted in human milk following use of ATRIDOX™. Because of the potential for serious adverse reactions in nursing infants from doxycycline, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. (See **WARNINGS** section)

Pediatrics:

The safety and effectiveness of ATRIDOX™ in pediatric patients have not been established. Oral doses of doxycycline in children up to 8 years of age have caused permanent discoloration of teeth.

ADVERSE REACTIONS

In clinical trials involving a total of 1436 patients, adverse experiences from all causalities were monitored across treatment groups.

In the Circulatory System category, 10 subjects (1.6%) in the ATRIDOX™ group were reported as having "unspecified essential hypertension." Only 1 subject (0.2%) in the Vehicle group, and none in the Scaling and Root Planing or Oral Hygiene groups were reported to have "unspecified essential hypertension." In all cases, the event occurred anywhere from 13 to 134 days post treatment. There is no known association of oral administration of doxycycline with essential hypertension.

Two patients in the polymer vehicle group and none in the ATRIDOX™ group (0.2% for both groups combined) reported adverse events consistent with a localized allergic response.

Sex, age, race and smoking status did not appear to be correlated with adverse events.

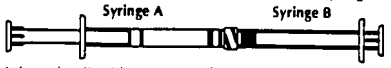
The following table lists the incidence of treatment-emergent adverse events from all-causalities, across all treatment groups, occurring in ≥1% of the entire study population.

Body System Verbatim Terms	Doxycycline n=609	Vehicle n=413	OH n=204	SRP n=210
Circulatory				
High blood pressure	1.6%	0.2%	0.0%	0.0%
Digestive				
Gum discomfort, pain or soreness; loss of attachment; increased pocket depth	18.1%	23.0%	20.1%	21.0%
Toothache, pressure sensitivity	14.3%	14.3%	10.3%	18.1%
Periodontal abscess, exudate, infection, drainage, extreme mobility, suppuration	9.9%	10.9%	10.3%	8.6%
Thermal tooth sensitivity	7.7%	8.5%	4.4%	6.7%
Gum inflammation, swelling, sensitivity	4.1%	5.8%	5.4%	5.7%
Soft tissue erythema, sore mouth, unspecified pain	4.3%	5.3%	2.7%	6.2%
Indigestion, upset stomach, stomachache	3.6%	4.1%	2.9%	3.8%
Diarrhea	3.3%	2.4%	1.0%	1.0%
Tooth mobility, bone loss	2.0%	0.7%	0.5%	2.4%
Periapical abscess, lesion	1.5%	1.9%	1.0%	0.5%
Aphthous ulcer, canker sores	0.7%	1.7%	1.0%	1.4%
Fistula	0.8%	1.5%	1.5%	1.0%
Endodontic abscess, pulpitis	1.5%	1.5%	0.0%	0.5%
Jaw pain	1.1%	0.5%	1.0%	1.9%
Tooth loss	0.8%	1.5%	1.5%	0.0%
Bleeding gums	1.0%	0.7%	0.0%	2.4%
Genitourinary				
Premenstrual tension syndrome	4.4%	3.1%	2.5%	3.3%
Ill-Defined Conditions				
Headache	27.3%	28.1%	23.5%	23.8%
Cough	3.6%	6.1%	2.9%	2.4%
Sleeplessness	3.4%	1.5%	2.0%	2.9%
Body aches, soreness	1.6%	1.2%	1.5%	1.4%
Nausea and vomiting	1.8%	0.7%	2.5%	0.5%
Fever	1.0%	1.9%	1.0%	1.9%
Injury & Poisoning				
Broken tooth	5.1%	4.1%	4.9%	5.7%
Mental				
Tension headache	1.8%	0.7%	0.0%	1.0%
Musculoskeletal				
Muscle aches	6.4%	4.6%	4.9%	3.3%
Backache	3.6%	5.3%	2.5%	6.2%
Pain in arms or legs	1.5%	2.2%	2.0%	2.4%
Lower back pain	1.6%	1.7%	0.5%	2.9%
Neck pain	1.3%	1.7%	1.0%	1.9%
Shoulder pain	1.0%	1.0%	1.5%	1.0%
Nervous System				
Ear infection	1.6%	1.9%	2.0%	0.0%
Respiratory				
Common cold	25.5%	25.2%	18.1%	16.7%
Flu, respiratory	6.1%	9.0%	3.9%	6.7%
Stuffy head, post nasal drip, congestion	5.6%	7.7%	2.9%	4.8%
Sore throat	5.7%	6.5%	2.0%	3.3%
Sinus infection	5.3%	2.7%	1.0%	1.9%
Flu	2.8%	2.9%	2.9%	3.3%
Bronchitis	2.3%	1.9%	1.5%	1.0%
Allergies	1.0%	1.0%	1.0%	1.9%
Skin & Subcutaneous Tissue				
Skin infection or inflammation	1.3%	1.0%	1.0%	1.0%

DOSAGE AND ADMINISTRATION

Preparation for Use

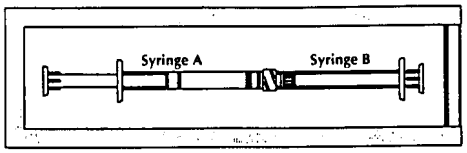
1. Remove the pouched product from refrigeration at least 15 minutes prior to mixing.
2. Couple Syringe A (liquid delivery system) and Syringe B (drug powder).



3. Inject the liquid contents of Syringe A (indicated by purple stripe) into Syringe B (doxycycline powder) and then push the contents back into Syringe A. This entire operation is one mixing cycle.
4. Complete 100 mixing cycles at a pace of one cycle per second using brisk strokes.

If immediate use is desired, skip to step 7.

5. **If necessary, the coupled syringes can be stored in the resealable pouch at room temperature for a maximum of three days.**

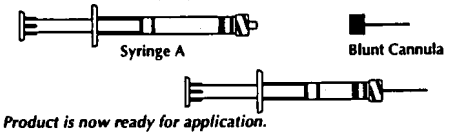


6. After storage, perform an additional ten mixing cycles just prior to use.

Continue with immediate use instructions.

7. The contents will be in **Syringe A** (indicated by purple stripe). Hold the coupled syringes vertically with **Syringe A** at the bottom. Pull back on the **Syringe A** plunger and allow the contents to flow down the barrel for several seconds.

8. Uncouple the two syringes and attach the blunt cannula to **Syringe A**.



Product is now ready for application.

Product Administration

ATRIDOX™ does not require local anesthesia for placement. Bend the cannula to resemble a periodontal probe and explore the periodontal pocket in a manner similar to periodontal probing. Keeping the cannula tip near the base of the pocket, express the product into the pocket until the formulation reaches the top of the gingival margin. Withdraw the cannula tip from the pocket. In order to separate the tip from the formulation, turn the tip of the cannula towards the tooth, press the tip against the tooth surface, and pinch the string of formulation from the tip of the cannula. Variations on this technique may be needed to achieve separation between ATRIDOX™ and cannula.

If desired, using an appropriate dental instrument, ATRIDOX™ may be packed into the pocket. Dipping the edge of the instrument in water before packing will help keep ATRIDOX™ from sticking to the instrument, and will help speed coagulation of ATRIDOX™. A few drops of water dripped onto the surface of ATRIDOX™ once in the pocket will also aid in coagulation. If necessary, add more ATRIDOX™ as described above and pack it into the pocket until the pocket is full.

Cover the pockets containing ATRIDOX™ with either Coe-Pak™ periodontal dressing or Octyldent™ dental adhesive.

Application of ATRIDOX™ may be repeated four months after initial treatment.

HOW SUPPLIED

ATRIDOX™ is available in a pouch containing a doxycycline hyclate syringe (50 mg), an ATRIGEL® Delivery System syringe (450 mg), and a blunt cannula.

Each ATRIDOX™ syringe system is intended for use in only one patient. Do not use if pouch has been previously opened or damaged.

Dosage Information

The final blended product is 500 mg of formulation containing 50.0 mg of doxycycline hyclate (doxycycline hyclate, 10%).

ATRIDOX™ is a variable dose product dependent on the size, shape, and number of pockets being treated.

Storage Conditions

Store at 2°-8°C (36°-46°F).

R_x Only

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ATRIDOX™ products are produced under one or more of these patents: U.S. 5324519, U.S. 4938763, U.S. 5278201
Manufactured by Atrix Laboratories, Inc. Exclusively for:
Block Drug Corporation
Jersey City, NJ 07302-3198

Part Number: 04076 Rev. 2 9/98
Product Number: 191007

BLOCK DRUG CORPORATION

Block Drug Corporation, Jersey City, NJ 07302-3198

To Order Call: 1-800-OK-BLOCK

ATRIDOX

(doxycycline hyclate, 10%)
in the ATRIGEL® Delivery System
for controlled release in
subgingival application

NDC 64410-191-00
NDC 64410-191-01

Exhibit 2

(APPROVAL LETTER)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-751

SEP - 3 1998

Atrix Laboratories, Inc.
Attention: Elaine Gazdeck
2579 Midpoint Drive
Fort Collins, CO 80525

Dear Ms. Gazdeck:

Please refer to your new drug application (NDA) dated March 31, 1997, received April 1, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Atridox™ (doxycycline hyclate, 10.0%) in the Atrigel® Delivery System* for Controlled Release in Subgingival Application *[63.3% N-methyl-2-pyrrolidone and 36.7% poly (DL-lactide)]. We note that this application is subject to the exception provisions of Section 125(d)(2) of Title 1 of the FDA Modernization Act of 1997.

We acknowledge receipt of your submissions dated March 9, April 10 and 24, May 11, and July 2 and 24, 1998. Your submission of July 2, 1998 constituted a full response to our April 7, 1998 action letter. The user fee goal date for this application is January 6, 1999.

This new drug application provides for the use of Atridox for the treatment of chronic adult periodontitis for a gain in clinical attachment, reduction in probing depth, and reduction in bleeding on probing.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the enclosed approved labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the enclosed approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavyweight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 50-751." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Roy Blay, Ph.D., Project Manager, at (301) 827-2020.

Sincerely,

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

ENCLOSURE

Exhibit 3

(PATENT)

United States Patent [19]

Dunn et al.

[11] **Patent Number: 4,938,763**

[45] **Date of Patent: Jul. 3, 1990**

[54] **BIODEGRADABLE IN-SITU FORMING IMPLANTS AND METHODS OF PRODUCING THE SAME**

[76] Inventors: **Richard L. Dunn**, 451 Boardwalk Dr. RLD, Apt. 501, Fort Collins, Colo. 80526; **James P. English**, 2500 Melinda Cir., Birmingham, Ala. 35214; **Donald R. Cowsar**, 4657 Round Forest Dr., Birmingham, Ala. 35213; **David P. Vanderbilt**, 1049-D Beacon Parkway East, Birmingham, Ala. 35204

[21] Appl. No.: **252,645**

[22] Filed: **Oct. 3, 1988**

[51] **Int. Cl.**[5] **A61K 9/22**

[52] **U.S. Cl.** **604/891.1**

[58] **Field of Search** ..... 600/37; 433/180, 201.1, 433/228.1; 604/890.1, 891.1, 27, 48, 49, 54, 93; 424/426, 435; 514/900; 128/156, DIG. 8, DIG. 21, 89 R; 623/11, 16; 606/76, 77

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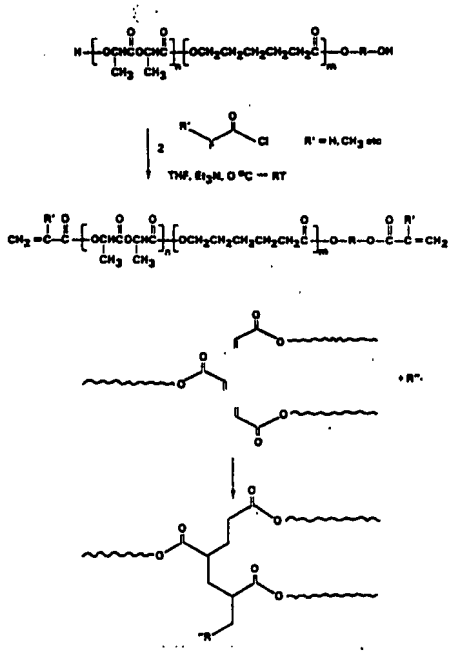
Primary Examiner—Stephen C. Pellegrino
Assistant Examiner—Sharon Rose
Attorney, Agent, or Firm—Needle & Rosenberg

[57] **ABSTRACT**

A biodegradable polymer is provided for use in providing syringeable, in-situ forming, solid biodegradable implants for animals. The polymer is placed into the animal in liquid form and cures to form the implant in-situ. A thermoplastic system to form said implant comprises the steps of dissolving a non-reactive polymer in biocompatible solvent to form a liquid, placing the liquid within the animal, and allowing the solvent to dissipate to produce the implant. An alternative, thermosetting system comprises mixing together effective amounts of a liquid acrylic ester terminated, biodegradable prepolymer and a curing agent, placing the liquid mixture within an animal and allowing the prepolymer to cure to form the implant. Both systems provide a syringeable, solid biodegradable delivery system by the addition of an effective level of biologically active agent to the liquid before injection into the body.

19 Claims, 2 Drawing Sheets



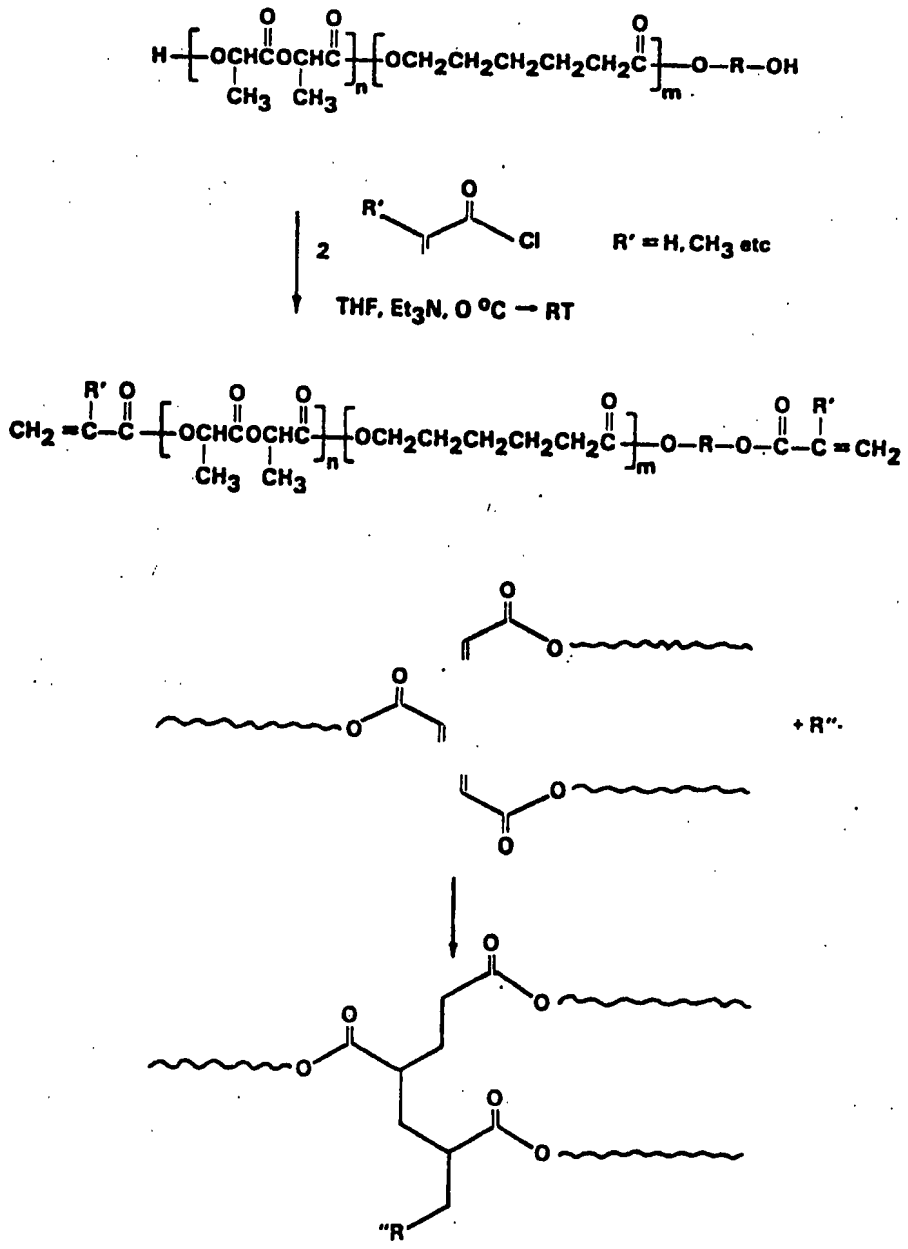
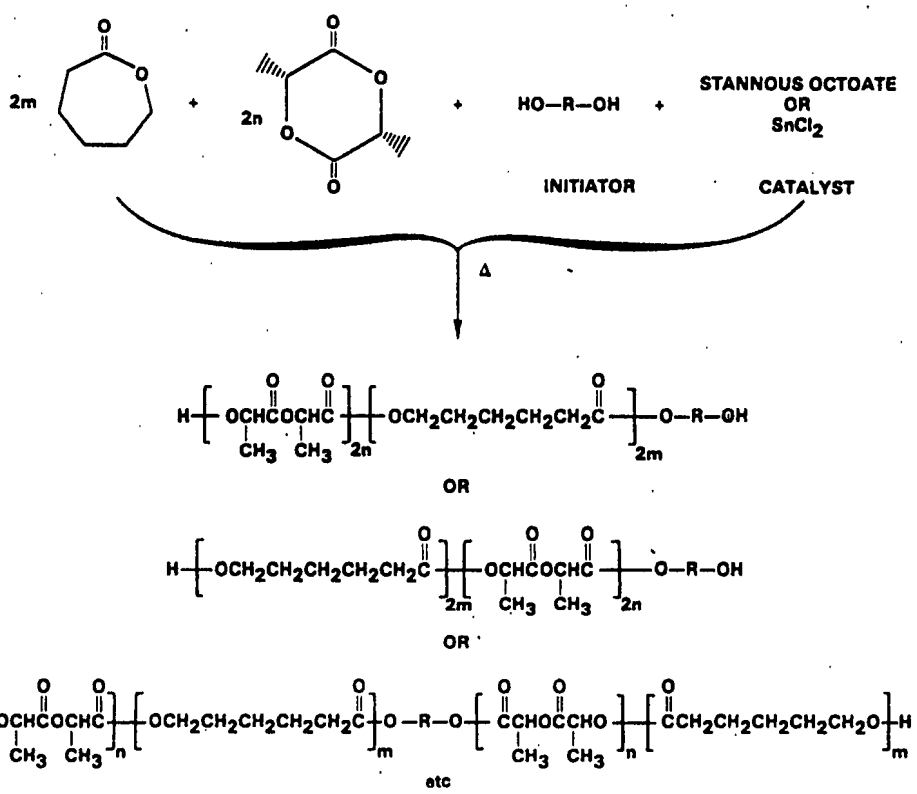


FIG.1

FIG. 2


2m
2n
HO—R—OH
STANNOUS OCTOATE
OR
$SnCl_2$
INITIATOR
CATALYST
Δ
OR
OR
etc

BIODEGRADABLE IN-SITU FORMING IMPLANTS AND METHODS OF PRODUCING THE SAME

BACKGROUND OF THE INVENTION

The present invention relates to a method and composition for producing biodegradable polymers, and more particularly to the use of such polymers for providing syringeable, in-situ forming, solid, biodegradable implants.

Biodegradable polymers have been used for many years in medical applications. These include sutures, surgical clips, staples, implants, and drug delivery systems. The majority of these biodegradable polymers have been thermoplastic materials based upon glycolide, lactide, ϵ–caprolactone, and copolymers thereof. Typical examples are the polyglycolide sutures described in U.S. Pat. No. 3,297,033 to Schmitt, the poly(L-lactide-co-glycolide) sutures described in U.S. Pat. No. 3,636,956 to Schneider, the poly(L-lactide-co-glycolide) surgical clips and staples described in U.S. Pat. No. 4,523,591 to Kaplan et al., and the drug-delivery systems described in U.S. Pat. No. 3,773,919 to Boswell et al., U.S. Pat. No. 3,887,699 to Yolles, U.S. Pat. No. 4,155,992 to Schmitt, U.S. Pat. No. 4,379,138 to Pitt et al., and U.S. Pat. Nos. 4,130,639 and 4,186,189 to Shalaby et al.

All of the biodegradable polymers described in these patents are thermoplastic materials. Consequently, they can be heated and formed into various shapes such as fibers, clips, staples, pins, films, etc. Only when heated above their melting point do these polymers become liquid. During their normal use, they are solids.

Thermoset biodegradable polymers have also been previously described for use in medical applications. These polymers have been formed by crosslinking reactions which lead to high-molecular-weight materials that do not melt or form flowable liquids at high temperatures. Typical examples of these materials are the crosslinked polyurethanes described in U.S. Pat. No. 2,933,477 to Hostettler and U.S. Pat. No. 3,186,971 to Hostettler et al. Copolymers based on ϵ-caprolactone and L-lactide or DL-lactide crosslinked via peroxide initiators were described in U.S. Pat. Nos. 4,045,418 and 4,057,537, both to Sinclair. Crosslinked caprolactone copolymers have been prepared by incorporation of a bislactone into a monomer feed, as described in U.S. Pat. No. 4,379,138 to Pitt et al. Trihydroxy-functional copolymers of ϵ-caprolactone and ϵ-valerolactone have been crosslinked with diisocyanates, thereby affording biodegradable polymers, as described in Pitt et al., J. Polym. Sci.: Part A: Polym Chem. 25:955–966; 1987. These polymers are also solids when crosslinked or cured.

Although these two classes of biodegradable polymers have many useful biomedical applications, there are several important limitations to their use in the body where body is defined as that of humans, animals, birds, fish, and reptiles. Because these polymers are solids, all instances involving their use have required initially forming the polymeric structures outside the body, followed by insertion of the solid structure into the body. For example, sutures, clips, and staples are all formed from thermoplastic biodegradable polymers prior to use. When inserted into the body, they retain their original shape rather than flow to fill voids or cavities where they may be most needed.

Similarly, drug-delivery systems using these biodegradable polymers have to be formed outside the body. In such instances, the drug is incorporated into the polymer and the mixture shaped into a certain form such a cylinder, disc, or fiber for implantation. With such solid implants, the drug-delivery system has to be inserted into the body through an incision. These incisions are often larger than desired by the medical profession and lead to a reluctance of the patients to accept such an implant or drug-delivery system.

The only way to avoid the incision with these polymers is to inject them as small particles, microspheres, or microcapsules. These may or may not contain a drug which can be released into the body. Although these small particles can be injected into the body with a syringe, they do not always satisfy the demand for a biodegradable implant. Because they are particles, they do not form a continuous film or solid implant with the structural integrity needed for certain prostheses. When inserted into certain body cavities such as the mouth, a periodontal pocket, the eye, or the vagina where there is considerable fluid flow, these small particles, microspheres, or microcapsules are poorly retained because of their small size and discontinuous nature. In addition, microspheres or microcapsules prepared from these polymers and containing drugs for release into the body are sometimes difficult to produce on a large scale, and their storage and injection characteristics present problems. Furthermore, one other major limitation of the microcapsule or small-particle system is their lack of reversibility without extensive surgical intervention. That is, if there are complications after they have been injected, it is considerably more difficult to remove them from the body than with solid implants.

Therefore, there exists a need for a method and composition which provides a biodegradable, polymeric structure useful in overcoming the above-described limitations.

There exists a further need for a method and composition for providing syringeable, in-situ forming, solid, biodegradable implants which can be used as prosthetic devices and/or controlled delivery systems.

Moreover, there exists a need for such a method and composition which can provide implants having a range of properties from soft to rigid, so as to be usable with both soft and hard tissue.

SUMMARY OF THE PRESENT INVENTION

The present invention relates to the production and use of biodegradable polymers as prosthetic implants and controlled-release, drug-delivery systems which can be administered as liquids via, for example, a syringe and needle, but which coagulate or cure ("set") shortly after dosing to form a solid. The implants are biodegradable because they are made from biodegradable polymers and copolymers comprising two types of polymer systems: thermoplastic and thermosetting.

A thermoplastic system is provided in which a solid, linear-chain, biodegradable polymer or copolymer is dissolved in a solvent, which is nontoxic and water miscible, to form a liquid solution. Once the polymer solution is placed into the body where there is sufficient water, the solvent dissipates or diffuses away from the polymer, leaving the polymer to coagulate or solidify into a solid structure. The placement of the solution can be anywhere within the body, including soft tissue such

as muscle or fat, hard tissue such as bone, or a cavity such as the periodontal, oral, vaginal, rectal, nasal, or a pocket such as a periodontal pocket or the cul-de-sac of the eye. For drug-delivery systems, the biologically active agent is added to the polymer solution where it is either dissolved to form a homogeneous solution or dispersed to form a suspension or dispersion of drug within the polymeric solution. When the polymer solution is exposed to body fluids or water, the solvent diffuses away from the polymer-drug mixture and water diffuses into the mixture where it coagulates the polymer thereby trapping or encapsulating the drug within the polymeric matrix as the implant solidifies. The release of the drug then follows the general rules for diffusion or dissolution of a drug from within a polymeric matrix.

Another embodiment of the invention is also provided, namely, a thermosetting system comprising the synthesis of crosslinkable polymers which are biodegradable and which can be formed and cured in-situ. The thermosetting system comprises reactive, liquid, oligomeric polymers which contain no solvents and which cure in place to form solids, usually with the addition of a curing catalyst.

The multifunctional polymers useful in the thermosetting system are first synthesized via copolymerization of either DL-lactide or L-lactide with ϵ-caprolactone using a multifunctional polyol initiator and a catalyst to form polyolterminated prepolymers. The polyolterminated prepolymers are then converted to acrylic ester-terminated prepolymers, preferably by acylation of the alcohol terminus with acryloyl chloride via a Sohotten-Baumann-like technique, i.e., reaction of acyl halides with alcohols. The acrylic ester-terminated prepolymers may also be synthesized in a number of other ways, including but not limited to, reaction of carboxylic acids (i.e., acrylic or methacrylic acid) with alcohols, reaction of carboxylic acid esters (i.e., methyl acrylate or methyl methacrylate) with alcohols by transesterification, and reaction of isocyanatoalkyl acrylates (i.e.. isocyanatoethyl methacrylate) with alcohols.

The liquid acrylic-terminated prepolymer is cured, preferably by the addition of benzoyl peroxide or azobisisobutyronitrile, to a more solid structure. Thus, for an implant utilizing these crosslinkable polymers, the catalyst is added to the liquid acrylic-terminated prepolymer immediately prior to injection into the body. Once inside the body, the crosslinking reaction will proceed until sufficient molecular weight has been obtained to cause the polymer to solidify. The liquid prepolymer, when injected, will flow into the cavity or space in which it is placed and assume that shape when it solidifies. For drug delivery utilizing this system, biologically active agents are added to the liquid polymer systems in the uncatalyzed state.

In both the thermoplastic and the thermosetting systems, the advantages of liquid application are achieved. For example, the polymer may be injected via syringe and needle into a body while it is in liquid form and then left in-situ to form a solid biodegradable implant structure. The need to form an incision is eliminated, and the implant will assume the shape of its cavity. Furthermore, a drug-delivery vehicle may be provided by adding a biologically active agent to the liquid prior to injection. Once the implant is formed, it will release the agent to the body and then biodegrade. The term "biologically active agent" means a drug or some other substance capable of producing an effect on a body.

It is an object of the present invention, therefore, to provide a method and composition for producing biodegradable polymers.

It is also an object of the present invention to provide such a polymer which may be useful in producing syringeable, in-situ forming, solid biodegradable implants.

It is a further object of the present invention to provide such an implant which can be used in a controlled-release delivery system for biological agents.

It is a further object of the present invention to provide implants having a range of properties from soft and elastomeric to hard and rigid, so as to be usable with both soft and hard tissue.

BRIEF DESCRIPTION OF THE FIGURES AND TABLES

FIG. 1 illustrates the synthesis of acrylate-terminated prepolymers and subsequent crosslinking by free-radical initiators;

FIG. 2 illustrates structures for the random copolymer of ϵ-caprolactone and L-lactide initiated with a diol;

Table 1 is a summary of the bifunctional PLC prepolymers synthesized;

Table 2 is a summary of the acrylic ester terminated prepolymers synthesized; and

Table 3 is a summary of curing studies.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to biodegradable, in-situ forming implants and methods for producing the same. The present invention also relates to a liquid biodegradable polymeric delivery system that can be injected into a body where it forms a solid and releases a biologically active agent at a controlled rate. Two types of biodegradable polymeric systems are described: thermoplastic polymers dissolved in a biocompatible solvent and thermosetting polymers that are liquids without the use of solvents.

A. Thermoplastic System

A thermoplastic system is provided in which a solid, linear-chain, biodegradable polymer is dissolved in a biocompatible solvent to form a liquid, which can then be administered via a syringe and needle. Examples of biodegradable polymers which can be used in this application are polylactides, polyglycolides, polycaprolactones, polyanhydrides, polyamides, polyurethanes, polyesteramides, polyorthoesters, polydioxanones, polyacetals, polyketals, polycarbonates, polyorthocarbonates, polyphosphazenes, polyhydroxybutyrates, polyhydroxyvalerates, polyalkylene oxalates, polyalkylene succinates, poly(malic acid), poly(amino acids), polyvinylpyrrolidone, polyethylene glycol, polyhydroxycellulose, chitin, chitosan, and copolymers, terpolymers, or combinations or mixtures of the above materials. The preferred polymers are those which have a lower degree of crystallization and are more hydrophobic. These polymers and copolymers are more soluble in the biocompatible solvents than the highly crystalline polymers such as polyglycolide and chitin which also have a high degree of hydrogen-bonding. Preferred materials with the desired solubility parameters are the polylactides, polycaprolactones, and copolymers of these with glycolide in which there are more amorphous regions to enhance solubility.

It is also preferred that the solvent for the biodegradable polymer be non-toxic, water miscible, and otherwise biocompatible. Solvents that are toxic should not be used to inject any material into a living body. The solvents must also be biocompatible so that they do not cause severe tissue irritation or necrosis at the site of implantation. Furthermore, the solvent should be water miscible so that it will diffuse quickly into the body fluids and allow water to permeate into the polymer solution and cause it to coagulate or solidify. Examples of such solvents include N-methyl-2-pyrrolidone, 2-pyrrolidone, ethanol, propylene glycol, acetone, methyl acetate, ethyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid, and 1-dodecylazacycloheptan-2-one. The preferred solvents are N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide, and acetone because of their solvating ability and their compatibility.

The solubility of the biodegradable polymers in the various solvents will differ depending upon their crystallinity, their hydrophilicity, hydrogen-bonding, and molecular weight. Thus, not all of the biodegradable polymers will be soluble in the same solvent, but each polymer or copolymer should have its optimum solvent. Lower molecular-weight polymers will normally dissolve more readily in the solvents than high-molecular-weight polymers. As a result, the concentration of a polymer dissolved in the various solvents will differ depending upon type of polymer and its molecular weight. Conversely, the higher molecular-weight polymers will normally tend to coagulate or solidify faster than the very low-molecular-weight polymers. Moreover the higher molecular-weight polymers will tend to give higher solution viscosities than the low-molecular-weight materials. Thus for optimum injection efficiency, the molecular weight and the concentration of the polymer in the solvent have to be controlled.

For example, low-molecular-weight polylactic acid formed by the condensation of lactic acid will dissolve in N-methyl-2-pyrrolidone(NMP) to give a 73% by weight solution which still flows easily through a 23-gauge syringe needle, whereas a higher molecular-weight poly(DL-lactide) (DL-PLA) formed by the additional polymerization of DL-lactide gives the same solution viscosity when dissolved in NMP at only 50% by weight. The higher molecular-weight polymer solution coagulates immediately when placed into water. The low-molecular-weight polymer solution, although more concentrated, tends to coagulate very slowly when placed into water.

For polymers that tend to coagulate slowly, a solvent mixture can be used to increase the coagulation rate. Thus one liquid component of the mixture is a good solvent for the polymer, and the other component is a poorer solvent or a nonsolvent. The two liquids are mixed at a ratio such that the polymer is still soluble but precipitates with the slightest increase in the amount of non-solvent, such as water in a physiological environment. By necessity, the solvent system must be miscible with both the polymer and water. An example of such a binary solvent system is the use of NMP and ethanol for low-molecular-weight DL-PLA. The addition of ethanol to the NMP/polymer solution increases its coagulation rate significantly.

It has also been found that solutions containing very high concentrations of high-molecular-weight polymers sometimes coagulate or solidify slower than more dilute solutions. It is suspected that the high concentration of polymer impedes the diffusion of solvent from within the polymer matrix and consequently prevents the permeation of water into the matrix where it can precipitate the polymer chains. Thus, there is an optimum concentration at which the solvent can diffuse out of the polymer solution and water penetrates within to coagulate the polymer.

In one envisioned use of the thermoplastic system, the polymer solution is placed in a syringe and injected through a needle into the body. Once in place, the solvent dissipates, the remaining polymer solidifies, and a solid structure is formed. The implant will adhere to its surrounding tissue or bone by mechanical forces and can assume the shape of its surrounding cavity. Thus, the biodegradable polymer solution can be injected subdermally like collagen to build up tissue or to fill in defects. It can also be injected into wounds including burn wounds to prevent the formation of deep scars. Unlike collagen, the degradation time of the implant can be varied from a few weeks to years depending upon the polymer selected and its molecular weight. The injectable polymer solution can also be used to mend bone defects or to provide a continuous matrix when other solid biodegradable implants such as hydroxyapatite plugs are inserted into bone gaps. The injectable system can also be used to adhere tissue to tissue or other implants to tissue by virtue of its mechanical bonding or encapsulation of tissue and prosthetic devices.

Another envisioned use of the thermoplastic system is to provide a drug-delivery system. In this use, a bioactive agent is added to the polymer solution prior to injection, and then the polymer/solvent/agent mixture is injected into the body. In some cases, the drug will also be soluble in the solvent, and a homogenous solution of polymer and drug will be available for injection. In other cases, the drug will not be soluble in the solvent, and a suspension or dispersion of the drug in the polymer solution will result. This suspension or dispersion can also be injected into the body. In either case, the solvent will dissipate and the polymer will solidify and entrap or encase the drug within the solid matrix. The release of drug from these solid implants will follow the same general rules for release of a drug from a monolithic polymeric device. The release of drug can be affected by the size and shape of the implant, the loading of drug within the implant, the permeability factors involving the drug and the particular polymer, and the degradation of the polymer. Depending upon the bioactive agent selected for delivery, the above parameters can be adjusted by one skilled in the art of drug delivery to give the desired rate and duration of release.

The term drug or bioactive (biologically active) agent as used herein includes without limitation physiologically or pharmacologically active substances that act locally or systemically in the body. Representative drugs and biologically active agents to be used with the syringeable, in-situ forming solid implant systems include, without limitation, peptide drugs, protein drugs, desensitizing agents, antigens, vaccines, anti-infectives, antibiotics, antimicrobials, antiallergenics, steroidal anti-inflammatory agents, decongestants, miotics, anticholinergios, sympathomimetics, sedatives, hypnotics, psychic energizers, tranquilizers, androgenic steroids, estrogens, progestational agents, humoral agents, prostaglandins, analgesics, antispasmodics, antimalarials,

antihistamines, cardioactive agents, non-steroidal anti-inflammatory agents, antiparkinsonian agents, antihypertensive agents, β-adrenergic blocking agents, nutritional agents, and the benzophenanthridine alkaloids. To those skilled in the art, other drugs or biologically active agents that can be released in an aqueous environment can be utilized in the described injectable delivery system. Also, various forms of the drugs or biologically active agents may be used. These include without limitation forms such as uncharged molecules, molecular complexes, salts, ethers, esters, amides, etc., which are biologically activated when injected into the body.

The amount of drug or biologically active agent incorporated into the injectable, in-situ, solid forming implant depends upon the desired release profile, the concentration of drug required for a biological effect, and the length of time that the drug has to be released for treatment. There is no critical upper limit on the amount of drug incorporated into the polymer solution except for that of an acceptable solution or dispersion viscosity for injection through a syringe needle. The lower limit of drug incorporated into the delivery system is dependent simply upon the activity of the drug and the length of time needed for treatment.

In all cases, the solid implant formed within the injectable polymer solution will slowly biodegrade within the body and allow natural tissue to grow and replace the impact as it disappears. Thus, when the material is injected into a soft-tissue defect, it will fill that defect and provide a scaffold for natural collagen tissue to grow. This collagen tissue will gradually replace the biodegradable polymer. With hard tissue such as bone, the biodegradable polymer will support the growth of new bone cells which will also gradually replace the degrading polymer. For drug-delivery systems, the solid implant formed from the injectable system will release the drug contained within its matrix at a controlled rate until the drug is depleted. With certain drugs, the polymer will degrade after the drug has been completely released. With other drugs such as peptides or proteins, the drug will be completely released only after the polymer has degraded to a point where the non-diffusing drug has been exposed to the body fluids.

B. Thermosetting System

The injectable, in-situ forming biodegradable implants can also be produced by crosslinking appropriately functionalized biodegradable polymers. The thermosetting system comprises reactive, liquid, oligomeric polymers which cure in place to form solids, usually with the addition of a curing catalyst. Although any of the biodegradable polymers previously described for the thermoplastic system can be used, the limiting criteria is that low-molecular-weight oligomers of these polymers or copolymers must be liquids and they must have functional groups on the ends of the prepolymer which can be reacted with acryloyl chloride to produce acrylic ester capped prepolymers.

The preferred biodegradable system is that produced from poly(DL-lactide-co-caprolactone), or "DL-PLC". Low-molecular-weight polymers or oligomers produced from these materials are flowable liquids at room temperature. Hydroxy-terminated PLC prepolymers may be synthesized via copolymerization of DL-lactide or L-lactide and ε-caprolactone with a multifunctional polyol initiator and a catalyst. Catalysts useful for the preparation of these prepolymers are preferably basic or neutral ester-interchange (transesterification) catalysts. Metallic esters of carboxylic acids containing up to 18 carbon atoms such as formic, acetic, lauric, stearic, and benzoic are normally used as such catalysts. Stannous octoate and stannous chloride are the preferred catalysts, both for reasons of FDA compliance and performance.

If a bifunctional polyester is desired, a bifunctional chain initiator such as ethylene glycol is employed. A trifunctional initiator such as trimethylolpropane produces a trifunctional polymer, etc. The amount of chain initiator used determines the resultant molecular weight of the polymer or copolymer. At high concentrations of chain initiator, the assumption is made that one bifunctional initiator molecule initiates only one polymer chain. On the other hand, when the concentration of bifunctional initiator is very low, each initiator molecule can initiate two polymer chains. In any case, the polymer chains are terminated by hydroxyl groups, as seen in FIG. 1. In this example, the assumption has been made that only one polymer chain is initiated per bifunctional initiator molecule. This assumption allows the calculation of a theoretical molecular weight for the prepolymers.

A list of the bifunctional PLC prepolymers that were synthesized is given in Table 1. Appropriate amounts of DL-lactide, ε-caprolactone, and ethylene glycol were combined in a flask under nitrogen and then heated in an oil bath at 155° C. to melt and mix the monomers. The copolymerizations were then catalyzed by the addition of 0.03 to 0.05 wt % $SnCl_2$. The reaction was allowed to proceed overnight. The hydroxyl numbers of the prepolymers were determined by standard titration procedure. The Gardner-Holdt viscosities of the liquid prepolymers were also determined using the procedures outlined in ASTM D 1545. The highest molecular-weight prepolymer (MW=5000) was a solid at room temperature; therefore, its Gardner-Holdt viscosity could not be determined.

The diol prepolymers were converted to acrylic-ester-capped prepolymers via a reaction with acryloyl chloride under Schotten-Baumann-like conditions, as seen in FIG. 2 and summarized in Table 2. Other methods of converting the diol prepolymers to acrylic-ester-capped prepolymers may also be employed.

Both THF and dichloromethane were evaluated as solvents in the acylation reactions. Several problems were encountered when THF was used as the solvent. The triethylamine hydrochloride formed as a by-product in the reaction was so finely divided that it could not be efficiently removed from the reaction mixture by filtration. Triethylamine hydrochloride ($Et_3N.HCl$) has been reported to cause polymerization of acrylic species (U.S. Pat. No. 4,405,798). In several instances, where attempts to remove all of the $Et_3N.HCl$ failed, the acrylic-ester-capped prepolymers gelled prematurely. Thus, to effectively remove all of the $Et_3N.HCl$, it was necessary to extract the prepolymers with water. For reactions carried out in THF, it is preferred that one first evaporate the THF in vacuo, redissolve the oil in CH_2Cl_2, filter out the $Et_3N.HCl$, and then extract the CH_2Cl_2 layer with water. Stable emulsions were sometimes encountered during extraction. The acylations were later carried out in CH_2Cl_2 instead of THF. The filtration of $Et_3N.HCl$ from the reaction mixture was found to be much easier using this solvent, and the organic fraction could be extracted directly with water after filtration.

Both diol and acrylic prepolymers were examined by IR and ^1H NMR spectroscopy. The salient feature of the IR spectra of diol prepolymers is a prominent O-H stretch centered at approximately 3510 cm^{-1}. Upon acylation, the intensity of the O-H stretch decreases markedly, and new absorbances at approximately 1640 cm^{-1} appear. These new absorbances are attributed to the C—C stretch associated with acrylic groups. Likewise, the presences of acrylic ester groups is apparent in the ^1H NMR spectra, the characteristic resonances for the vinyl protons falling in the range of 5.9 to 6.6 ppm.

The acrylic prepolymers and diol prepolymers were then cured, as summarized in Table 3. The general procedure for the curing of the prepolymers is now described: to 5.0 g of acrylic prepolymer contained in a small beaker was added a solution of benzoyl peroxide (BP) in approximately 1 mL of CH_2Cl_2. In some cases, fillers or additional acrylic monomers were added to the prepolymers prior to the introduction of the BP solution. The mixtures were stirred thoroughly and then poured into small petri dishes. The dishes were placed in a preheated vacuum oven for curing. Some of the samples were cured in air and not in vacuo, and these samples are so indicated in Table 3.

This thermosetting system may be used wherever a biodegradable implant is desired. For example, because the prepolymer remains a liquid for a short time after addition of the curing agent, the liquid prepolymer/curing agent mixture may be placed into a syringe and injected into a body. The mixture then solidifies in-situ, thereby providing an implant without an incision. Furthermore, a drug-delivery system may be provided by adding a biologically active agent to the prepolymer prior to injection. Once in-situ, the system will cure to a solid; eventually, it will biodegrade, and the agent will be gradually released.

DETAILED DESCRIPTION OF EXAMPLES

The following examples are set forth as representative of the present invention. These examples are not to be construed as limiting the scope of the invention as these and other equivalent embodiments will be apparent in view of the present disclosure, figures, and accompanying claims.

EXAMPLE 1

Poly(DL-lactic acid) was prepared by the simple polycondensation of lactic acid. No catalysts were used, and the reaction times were varied to produce polymers with different theoretical molecular weights. These polymers were designated as DL-PLA oligomers. A quantity of the solid oligomer was dissolved in NMP to give a 68:32 ratio of polymer to solvent. Sanguinarine chloride(SaCl), a benzophenanthridine alkaloid with antimicrobial activity especially toward periodontal pathogens, was added to the polymer solution to give a 2% by weight dispersion of the drug in the total mixture. The dispersion of drug and polymer solution was then injected into a dialysis tube (diameter of 11.5 mm) with a sterile disposable syringe without a needle. Each end of the 6-in. length of dialysis tubing was tied with a knot to prevent loss of the drug/polymer mass, and the tube with the injected material was placed in a pH 7 Sorenson's buffer receiving fluid maintained at 37° C. Upon immersion in the receiving fluid, the drug/polymer mass coagulated into a solid mass, and the drug began to be released from the polymer as indicated by an orange-red color in the receiving fluid. The quantity of solution injected into the dialysis tube was about 250 μL or about 100 mg of solids.

The dialysis tubing was selected to have a molecular-weight cutoff of about 3,500. With this molecular-weight cutoff, the SaCl released from the polymer could easily diffuse through the walls of the tubing, but any solid polymer would be retained. The dialysis tubing containing the drug/polymer matrix was removed frequently and placed in a bottle of fresh receiving fluid. The old receiving fluid containing the released drug was then acidified to a pH of 2.76 to convert all released drug to the iminium ion form of the drug, and the concentration of drug was determined by measuring the ultraviolet absorption (UV) at a wavelength of 237 nm. The cumulative mass of drug released and the cumulative fraction were then calculated and plotted as a function of time. Approximately 60% of the drug was released in the first day, 72% after 2 days, 85% after 5 days, 90% after 9 days, and 97% after 14 days.

EXAMPLE 2

Ethoxydihydrosanguinarine(SaEt), the ethanol ester of sanguinarine, was added to the same DL-PLA oligomer/NMP solution described in Example 1. SaEt dissolved in the polymer solution to give a homogenous solution of drug and polymer. Approximately 250 μL of the solution was added to receiving fluid and the release of drug measured as described in Example 1. The release of SaEt was slower than that for SaCl as expected because of its lower water solubility. After the first day, approximately 45% was released, 52% after 2 days, 60% after 5 days, 70% after 9 days, and 80% after 14 days.

EXAMPLE 3

Poly(DL-lactide) with an inherent viscosity of 0.08 dL/g and a theoretical molecular weight of 2,000 was prepared by the ring-opening polymerization of DL-lactide using lauryl alcohol as the initiator and stannous chloride as the catalyst. This polymer was then dissolved in NMP to give a 40% by weight polymer solution. SaCl was dispersed in the solution of this polymer in NMP to give a 1.5% by weight dispersion of the drug in the solution and the release rate determined as described in Example 1. The release rate of the drug from this higher molecular-weight polymer was slower than from the DL-PLA oligomer. After the first day, approximately 32% was released, 40% after 2 days, 45% after 5 days, and 50% after 15 days.

EXAMPLE 4

SaEt was added to the same polymer solution of DL-PLA in NMP as described in Example 3. A homogenous solution with the drug at 1.5% by weight was obtained. The release of drug from this solution determined using the same procedure described in Example 1 gave a much slower release of SaEt than from the DL-PLA oligomer. After the first day approximately 8% was released, 14% after 2 days, 20% after 5 days, 23% after 9 days, and 28% after 14 days.

EXAMPLE 5

The effect of drug loading on the release of drug from the polymer solutions were demonstrated by adding SaCl to a 40% by weight of DL-PLA oligomer in NMP. The drug was dispersed in the polymer solution to give 2, 7 and 14% by weight dispersions. The release of drug from these formulations using the same proce-

dure as described in Example 1 showed that the higher drug loadings gave a lower fractional rate of release as normally obtained for matrix delivery systems with diffusional release. The 2%-loaded formulation gave 65% release after 1 day, 75% after 2 days, and 88% after 5 days; the 7%-loaded formulation gave 48% release after 1 day, 52% after 2 days, and 58% after 5 days; and the 14%-loaded formulation gave 38% release after 1 day, 43% after 2 days, and 49% after 5 days.

EXAMPLE 6

Poly(DL-lactide-co-glycolide) was prepared by the ring-opening polymerization of a mixture of DL-lactide and glycolide using lauryl alcohol as the initiator and stannous chloride as the catalyst. The proportions of the two monomers were adjusted so that the final copolymer(DL-PLG) had a 50:50 ratio of the two monomers as determined by nuclear magnetic resonance spectrophotometry. The initiator was also adjusted to give a copolymer with a theoretical molecular weight of 1500 daltons. The copolymer was dissolved in NMP to give a 70% by weight polymer solution. SaCl was added to this solution to give a 2% by weight dispersion of the drug in the polymer solution. The release of drug from this formulation was determined using the same procedure described in Example 1. A much lower release rate was obtained from the copolymer than from the DL-PLA oligomer or DL-PLA 2000 molecular weight materials. After 2 days approximately 7% of the drug was released, 10% after 5 days, 12% after 7 days, and 16% after 14 days.

EXAMPLE 7

SaEt was added to the same solution of DL-PLG in NMP as described in Example 6 to give a 2% by weight solution of the drug. The release of drug from this formulation was determined by the same procedure as described previously. The release rate of SaEt from this formulation was identical to that for SaCl described in Example 6.

EXAMPLE 8

Tetracycline as the free base (TCB) was added to the same solution of DL-PLG in NMP as described in Example 6. The drug dissolved completely in the polymer solution to give a 2.4% by weight solution of the drug. The release of the drug from this formulation was determined by a similar procedure to that described in Example 1 except the receiving fluid was not acidified to a pH of 2.76 and the concentration of TCB was determined by UV absorption at the wavelength appropriate for the drug. The release of TCB from this formulation was more linear and at a much higher rate than that for SaCl or SaEt from the same copolymer. After 1 day approximately 44% of the drug was released, 54% after 2 days, 68% after 5 days, 73% after 6 days, 80% after 7 days, 87% after 9 days, 96% after 12 days, and 100% after 14 days.

EXAMPLE 9

Tetracycline as the hydrochloride salt (TCH) was added to the same solution of DL-PLG in NMP as described in Example 6. The salt form of the drug also dissolved completely in the polymer solution. The release of drug from this formulation was determined as described in Example 8 and found to be similar to that for the free base except for a slightly lower rate. After 1 day approximately 32% of the drug was released, 40% after 2 days, 57% after 5 days, 64% after 6 days, 75% after 7 days, 82% after 9 days, 92% after 12 days, and 100% after 14 days.

EXAMPLE 10

DL-PLA with an inherent viscosity of 0.26 dL/g and a theoretical molecular weight of approximately 10,000 daltons was prepared by the ring-opening polymerization of DL-lactide using lauryl alcohol as the initiator and stannous chloride as the catalyst. The polymer was dissolved in NMP to give a 50% by weight polymer solution. A quantity of the polymer solution (100 μL) was injected subdermally into rabbits, and the tissue reaction was compared to that of a USP negative plastic. The test sites were evaluated for signs of local irritation, in accordance with the Draize method, immediately after injection, at 1 and 6 hours post injection, and once daily thereafter until scheduled sacrifice at 7, 14 or 21 days. The reaction at the test sites was equivalent to that at the control USP negative plastic. The polymer solution (100 μL) was also administered subgingivally into sites created by dental extractions in Beagle dogs. Control sites were flushed with saline solution. The dogs were examined daily for signs of mortality, pharmacotoxic effects, body weights, and local gingival irritation. The animals were sacrificed at 15 and 21 days. No distinct differences were noted between the control and test sites.

EXAMPLE 11

DL-PLA with an inherent viscosity of 0126 dL/g and a molecular weight of about 10,000 was dissolved in NMP to give a 50% by weight polymer solution. SaCl was added to the polymer solution to give a 2.4% by weight dispersion. This material was loaded into a 1-cc disposable syringe fitted with a 23-gauge blunted-end syringe needle, and the material was inserted into the periodontal pocket of a greyhound dog. The material flowed easily out of the narrow syringe tip. The polymer precipitated or coagulated into a film or solid mass when it contacted the saliva and fluid within the pocket. The dog was observed over a time of 2 weeks during which the mass of material remained within the pocket, adhering to tissue surrounding the pocket, and slowly changing color from a light orange to a pale white. The crevicular fluid from the pocket containing the implant was sampled during this 2-week period using Periostrips which are small strips of paper that are placed at the entrance to the periodontal pocket to wick up small quantities of the crevicular fluid within the pocket. The volume of fluid collected is determined using a Periotron which measures the changes in conductance of the paper strip. The Periotron is calibrated before use with a known volume of serum. The paper strip containing the collected fluid is then extracted with a solution of 0.5% by volume of hydrochloric acid in methanol and injected into a liquid chromatograph where the quantity of drug is determined by reference to a known concentration of the same compound. The quantity of SaCl extracted from the paper strip is divided by the quantity of crevicular fluid collected to calculate the concentration of drug in the fluid. With this technique, the concentration of SaCl within the crevicular fluid from the periodontal pocket with the polymeric delivery system was determined to be almost constant during the 2 weeks of observation. The SaCl concentration in the crevicular fluid was 63.2 μg/mL after 3 days, 80.2

μg/mL after 7 days, 67.8 μg/mL after 10 days, and 70.5 μg/mL after 14 days.

EXAMPLE 12

An illustrative method for the synthesis of an acrylate terminated prepolymer is described. To an oven-dried, 500-mL, three-necked, round-bottom flask fitted with an addition funnel, gas inlet adapter, mechanical stirrer assembly, and rubber septum was added, under nitrogen, 100.0 g of difunctional hydroxy-terminated prepolymer and 200 mL of freshly distilled THF (from CaH_2). The flask was cooled in an ice bath, and 24 mL of dry triethylamine (0.95 equiv/equiv OH) was added via a syringe. The addition funnel was charged with 15.4 g of acryloyl chloride (0.95 equiv/equiv OH) in 15 mL of THF, and the solution was added dropwise to the stirred reaction mixture over 1 hour. The mixture was stirred overnight and allowed to reach room temperature. The precipitated triethylamine hydrochloride was removed by filtration, and the filtrate was evaporated in vacuo, affording a pale yellow oil, which was the acrylate-terminated prepolymer. The acylations employing CH_2Cl_2 as solvent were conducted in a similar manner. However, the reaction times at 0° C. were shortened to 1 hour, whereupon the reaction mixtures were allowed to reach room temperature over 1 hour. Et_3N^1HCl was filtered out, additional CH_2Cl_2 (approximately 800 mL) was added to the filtrate, and the filtrate was extracted several times with 250 mL portions of water. The organic layer was dried over $MgSO_4$/-Na_2SO_4, filtered, and reduced to an oil in vacuo. The bottles of acrylic prepolymers were wrapped in foil and stored in a refrigerator to safeguard against premature crosslinking.

TABLE 1

SUMMARY OF DIOL PREPOLYMERS SYNTHESIZED

Sample no.	Mole ratio of monomers to initiator (ethylene glycol = 1.0) DL-lactide	ε-caprolactone	Catalyst ($SnCl_2$), wt %	Theoretical M_n, daltons	Hydroxyl No., meq OH (56.1)/g Observed	Theoretical	Gardner Holdt viscosity, approx. Stokes (T = 22.2° C.)
C964-114-1	2.4	5.0	0.03	993	100	113	28.0
C964-124-1	6.1	32.8	0.05	5036	19.7	22.3	Solid
C964-128-1	2.5	5.0	0.03	993	103	113	28.2
C964-136-1	8.0	8.0	0.03	2128	48 (est.)	52.7	1375

TABLE 2

SUMMARY OF ACRYLIC ESTER TERMINATED PREPOLYMERS SYNTHESIZED

Sample no.	Diol precursor sample no.	Estimated concentration of acrylic groups, meq/g	Reaction Conditions Temp, °C.	Time, h	Solvent	Comments
C964-118-1	C964-114-1	1.78	O-RT	17	THF	No problems, stable.
C964-125-1	C964-114-1	1.78	O-RT	17	THF	Gelled. Overnight exposure to $Et_3N.HCl$ at RT.
C964-132-1	C964-128-1	1.84	0	2	THF	100 ppm MEHQ added before workup.
C964-137-1	C964-128-1	1.84	0	2	Et_2O	Difficult workup. Low yield.
C964-139-1	C964-136-1	0.81	0	2	THF	Gelled. Overnight exposure to residual $Et_3N.HCl$ in refrigerator.
C964-144-1	C964-136-1	0.81	0	1	CH_2Cl_2	No problems, stable.
C964-146-1	C964-124-1	0.33	0	1	CH_2Cl_2	No problems, stable.

TABLE 3

SUMMARY OF CURING STUDIES

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives, wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp, °C.	Time, h		
C964-120-1	C964-118-1	2.0	none	82	16	ND[a]	Rubbery, breaks when bent 180°, weak.
C964-120-2	C964-118-1	1.0	none	82	16	83	Less brittle than C964-120-1.
C964-121-1	C964-118-1	2.0	none	82	16	77	Rubbery, breaks when bent 180°, weak.
C964-121-2	C964-118-1	1.0	none	82	16	80	Slightly stronger than C964-121-1.
C964-121-3	C964-118-1	0.5	none	82	16	78	Slightly more elastic than C964-121-2.
C964-121-4	C964-118-1	0.1	none	82	16	69	Same as C964-121-3.
C964-122-1	C964-118-1	1.0	TMPTETA[b] 46	82	2.5	94	Less rubbery than C964-120 and C964-121; brittle.
C964-122-2	C964-118-1	0.5	TMPTETA 46	82	2.5	91	Same as C964-122-1, more flexible.
C964-122-3	C964-118-1	1.0	TMPTETA 175	82	2.5	95	Not rubbery at all, brittle, weak.
C964-122-4	C964-118-1	0.5	TMPTETA 175	82	2.5	93	Similar to C964-122-3.
C964-123-1	C964-118-1	0.1	TMPTETA 46	82	2.5	89	Rubbery, stronger than C964-120 and C964-121, not flexible.
C964-123-2	C964-118-1	0.25	TMPTETA 46	82	2.5	83	About the same as C964-123-1, may be more brittle.
C964-123-3	C964-118-1	0.1	TMPTETA 175	82	2.5	92	Not rubbery; strong, brittle.
C964-134-1	C964-132-1	0.05 (AIBN)[c]	none	60[d]	17	Liquid	No cure.
C964-134-2	C964-132-1	0.10 (AIBN)	none	60[d]	17	Liquid	No cure.
C964-134-3	C964-132-1	0.25 (AIBN)	none	60[d]	17	Liquid	No cure.
C964-134-4	C964-132-1	0.50 (AIBN)	none	60[d]	17	Liquid	No cure.
C964-134-5	C964-132-1	1.00 (AIBN)	none	60[d]	17	Liquid	Slightly thickened.
C964-135-1	C964-132-1	0.05	none	80[d]	17	Liquid	No cure.
C964-135-2	C964-132-1	0.10	none	80[d]	17	Liquid	No cure.
C964-135-3	C964-132-1	0.25	none	80[d]	17	Liquid	No cure.
C964-135-4	C964-132-1	0.50	none	80[d]	17	Liquid	No cure.
C964-135-5	C964-132-1	1.00	none	80[d]	17	Liquid	Slightly thickened.
C964-135-6	C964-128-1[e]	0.05	none	80[d]	17	Liquid	No cure.
C964-135-7	C964-128-1[e]	0.10	none	80[d]	17	Liquid	No cure.
C964-135-8	C964-128-1[e]	0.25	none	80[d]	17	Liquid	No cure.
C964-135-9	C964-128-1[e]	0.50	none	80[d]	17	Liquid	No cure.
C964-135-10	C964-128-1[e]	1.00	none	80[d]	17	Liquid	No cure.
C964-135-11	C964-124-1[e]	0.05	none	80[d]	17	ND	No cure.
C964-135-12	C964-124-1[e]	0.10	none	80[d]	17	ND	No cure.
C964-135-13	C964-124-1[e]	0.25	none	80[d]	17	ND	No cure.
C964-135-14	C964-124-1[e]	0.50	none	80[d]	17	ND	No cure.
C964-135-15	C964-124-1[e]	1.00	none	80[d]	17	ND	No cure.
C964-141-1	C964-137-1	0.10	none	80	1	66	Flexible elastomer.
C964-141-2	C964-137-1	0.25	none	80	1	71	Flexible elastomer.
C964-141-3	C964-137-1	0.50	none	80	1	72	Flexible elastomer.
C964-141-4	C964-137-1	1.00	none	80	1	72	Flexible elastomer.
C964-141-5	C964-128-1	0.10	none	80	1	Liquid	No cure.
C964-141-6	C964-128-1	0.25	none	80	1	Liquid	No cure.
C964-141-7	C964-128-1	0.50	none	80	1	Liquid	No cure.
C964-141-8	C964-128-1	1.00	none	80	1	Liquid	No cure.
C964-143-1	C964-137-1	0.25	Cab-o-Sil PTG, 5.0	80	1	74	No cure.
C964-143-2	C964-137-1	0.25	Cab-o-Sil PTG, 2.5	80	1	73	No cure.
C964-143-3	C964-137-1	0.25	L-PLA (IV = 0.8), 5.0	80	1	75	No cure.

TABLE 3-continued

SUMMARY OF CURING STUDIES

Sample no.	Acrylic prepolymer sample no.	Benzoyl peroxide wt %	Other additives, wt %	Curing conditions		Initial Shore A hardness	Comments
				Temp, °C.	Time, h		
C964-143-4	C964-137-1	0.25	L-PLA (IV = 0.8), 2.5	80	1	78	No cure.
C964-148-1	C964-144-1	0.05	none	80	17	Liquid	No cure.
C964-148-2	C964-144-1	0.10	none	80	17	Liquid	No cure.
C964-148-3	C964-144-1	0.25	none	80	2	66	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.
C964-148-4	C964-144-1	0.50	none	80	2	68	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.
C964-148-5	C964-144-1	1.00	none	80	2	67	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C964-148-5.
C964-148-6	C964-144-1	2.00	none	80	2	69	C964-148-4 and C964-148-6 were about the same in toughness, and both were better than C964-148-3 and C-964-148-5.
C964-149-1	C964-144-1	0.15	none	80	2	64	
C964-149-2	C964-144-1	0.20	none	80	2	64	
C964-149-3	C964-144-1	0.25	none	80	2	66	
C964-149-4	C964-144-1	0.15	Cab-o-Sil N70-TS 5.0	80	2	ND	Samples too porous, did not have any flat area for hardness measurement.
C964-149-5	C964-144-1	0.20	Cab-o-Sil N70-TS 5.0	80	2	ND	Samples too porous, did not have any flat area for hardness measurement.
C964-149-6	C964-144-1	0.25	Cab-o-Sil N70-TS 5.0	80	2	ND	Samples too porous, did not have any flat area for hardness measurement.
C964-150-1	C964-146-1	0.05	none	80	17	ND	Only partially cured.
C964-150-2	C964-146-1	0.10	none	80	2	72	Elastic, flexible, moderately strong.
C964-150-3	C964-146-1	0.25	none	80	2	57	Elastic, flexible, moderately strong.
C964-150-4	C964-146-1	0.50	none	80	2	56	Elastic, flexible, moderately strong.
C964-150-5	C964-146-1	1.00	none	80	2	50	Elastic, flexible, moderately strong.
C964-150-6	C964-146-1	2.00	none	80	2	51	Elastic, flexible, moderately stong.

[a]Results not determined.
[b]TMPETA = trimethylolpropane triethoxy triacrylate.
[c]AIBN = azobisisbutyronitrile.
[d]Cured in air at atmospheric pressure.
[e]Diol prepolymer used.

What is claimed is:

1. A method of forming an implant in-situ, in a living body, comprising the steps of:

(a) dissolving a non-reactive, water-insoluble polymer in a biocompatible, water-soluble solvent to form a liquid;

(b) placing said liquid within said body; and

(c) allowing said solvent to dissipate to produce a solid implant.

2. The method of claim 1, wherein said solvent is comprised of a binary solvent mixture having a first solvent capable of dissolving said polymer and a second solvent incapable of dissolving said polymer, said first and second solvents being present in said mixture at a ratio ouch that said polymer is soluble therein, so that said polymer is precipitated from said liquid upon the placing of said liquid within said animal, thereby resulting in an increase in said ratio of said second solvent to said first solvent.

3. The method of claim 1, and further comprising delivering said liquid in-situ through a needle.

4. The method of claim 3, wherein said polymer is a lactide polymer and said second solvent is selected from the group consisting of water, ethanol and propylene glycol.

5. The method of claim 1, and further comprising the step of adding an effective amount of biologically active agent to said liquid to provide an implant which releases said agent by diffusion, erosion or a combination of diffusion and erosion as said plant biodegrades.

6. The method of claim 5, wherein said implant is formed in a periodontal pocket in said body.

7. The method of claim 6, wherein said biologically-active agent is selected from the group consisting of benzophenanthridine alkaloid and tetracycline.

8. The method of claim 5, wherein said biologically-active agent comprises a benzophenanthridine alkaloid.

9. The method of claim 8, wherein said alkaloid comprises sanguinarine chloride.

10. The method of claim 8, wherein said alkaloid comprises ethoxydihydrosanguinarine.

11. The method of claim 5, wherein said biologically-active agent comprises tetracycline base.

12. The method of claim 5, wherein said biologically-active agent comprises tetracycline hydrochloride.

13. A biodegradable drug delivery implant for a body produced according to the method of claim 5.

14. The method of claim 1, wherein said polymer is biodegradable.

15. The method of claim 1, wherein said polymer is selected from the group consisting of polylactides, polyglycolides, polycaprolactones, polydioxanones, polycarbonates, polyhydroxybutyrates, polyalkylene oxalates, polyanhydrides, polyamides, polyesteramides, polyurethanes, polyacetals, polyketals, polyorthocarbonates, polyphosphazenes, polyhydroxyvalerates, polyalkylene succinates, poly(malic acid), poly(amino acids), chitin, chitosan, and polyorthoesters, and copolymers, terpolymers and combinations and mixtures thereof.

16. The method of claim 1, wherein said polymer is selected from the group consisting of polylactides, polycaprolactones and copolymers thereof with glycolide.

17. The method of claim 1, wherein said solvent is selected from the group consisting of N-methyl-2-pyrrolidone, 2-pyrrolidone, ethanol, propylene glycol, acetone, ethyl acetate, methyl acetate, methyl ethyl ketone, dimethylformamide, dimethyl sulfoxide, tetrahydrofuran, caprolactam, decylmethylsulfoxide, oleic acid and 1-dodecylazacycloheptan-2-one and combinations and mixtures thereof.

18. The method of claim 1, wherein said solvent is selected from the group consisting of N-methyl-2-pyrrolidone, 2-pyrrolidone, dimethyl sulfoxide and acetone, and a combination or mixture thereof.

19. A biodegradable implant for a body produced according to the method of claim 1.

* * * * *

Exhibit 4A

(REEXAMINATION CERTIFICATE)

US004938763B1

REEXAMINATION CERTIFICATE (2618th)

United States Patent [19]

[11] B1 4,938,763

Dunn et al.

[45] Certificate Issued Jul. 4, 1995

[54] **BIODEGRADABLE IN-SITU FORMING IMPLANTS AND METHOD OF PRODUCING THE SAME**

[75] Inventors: **Richard L. Dunn**, Fort Collins, Colo.; **James P. English**, Birmingham, Ala.; **Donald R. Cowsar**, Birmingham, Ala.; **David P. Vanderbilt**, Birmingham, Ala.

[73] Assignee: **Atrix Laboratories, Inc.**, Fort Collins, Colo.

Reexamination Request:
No. 90/003,037, Apr. 27, 1993

Reexamination Certificate for:

Patent No.:	**4,938,763**
Issued:	**Jul. 3, 1990**
Appl. No.:	**252,645**
Filed:	**Oct. 3, 1988**

[51] **Int. Cl.**[6] **A61K 9/22**
[52] **U.S. Cl.** **604/891.1**
[58] **Field of Search** ..... 424/422, 426, 435; 523/105, 113; 514/900; 524/173, 113, 361, 386, 391, 233; 525/937; 600/37; 433/180, 201.1, 228.1; 604/890.1, 891.1, 27, 48, 49, 54, 93; 128/DIG. 8, DIG. 21; 623/11, 16; 606/76, 77

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Primary Examiner—C. Fred Rosenbaum

[57] **ABSTRACT**

A biodegradable polymer is provided for use in providing syringeable, in-situ forming, solid biodegradable implants for animals. The polymer is placed into the animal in liquid form and cures to form the implant in-situ. A thermoplastic system to form said implant comprises the steps of dissolving a non-reactive polymer in biocompatible solvent to form a liquid, placing the liquid within the animal, and allowing the solvent to dissipate to produce the implant. An alternative, thermosetting system comprises mixing together effective amounts of a liquid acrylic ester terminated, biodegradable prepolymer and a curing agent, placing the liquid mixture within an animal and allowing the prepolymer to cure to form the implant. Both systems provide a syringeable, solid biodegradable delivery system by the addition of an effective level of biologically active agent to the liquid before injection into the body.

REEXAMINATION CERTIFICATE ISSUED UNDER 35 U.S.C. 307

THE PATENT IS HEREBY AMENDED AS INDICATED BELOW.

Matter enclosed in heavy brackets [ ] appeared in the patent, but has been deleted and is no longer a part of the patent; matter printed in italics indicates additions made to the patent.

AS A RESULT OF REEXAMINATION, IT HAS BEEN DETERMINED THAT:

Claim 14 is cancelled.

Claims 1, 2, 4 and 5 are determined to be patentable as amended.

Claims 3, 6—13 and 15–19, dependent on an amended claim, are determined to be patentable.

New claim 20 is added and determined to be patentable.

1. A method of forming [an] *a biodegradable* implant in-situ, in a living body, comprising the steps of:

(a) dissolving a non-reactive, [water-insoluble] *thermoplastic* polymer *that is water-insoluble and is biodegradable by simple or enzymatically catalyzed hydrolysis*, in a biocompatible, water-soluble solvent to form a liquid;

(b) placing said liquid within said body; and

(c) allowing said [solvent to dissipate to produce a] *liquid to contact body fluid to dissipate or diffuse the solvent into the body fluid and cause the thermoplastic polymer to coagulate or solidify to produce the biodegradable* solid implant.

2. The method of claim 1, wherein said solvent is comprised of a binary solvent mixture having a first solvent capable of dissolving said polymer and a second solvent incapable dissolving said polymer, said first and second solvents being present in said mixture at a ratio [ouch] *such* that said polymer is soluble therein, so that said polymer is precipitated from said liquid upon the placing of said liquid within said animal, thereby resulting in an increase in said ratio of said second solvent to said first solvent.

4. The method of claim [3] *2* wherein said polymer is a lactide polymer and said second solvent is selected from the group consisting of water, ethanol and propylene glycol.

5. The method of claim 1, and further comprising the step of adding an effective amount of biologically active agent to said liquid to provide an implant which releases said agent by diffusion, erosion or a combination of diffusion and erosion as said [plant biodegrade] *implant biodegrades*.

20. A method according to claim 5 wherein the biologically active agent comprises a protein or peptide drug.

* * * * *

Exhibit 4B

(RECEIPT FOR FIRST MAINTENANCE FEE PAYMENT)

MG 8905.070 USA JAN '94

UNITED STATES DEPARTMENT OF COMMERCE
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75N4/0127
COMPUTER PACKAGES ANNUITY SERVICE INC.
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ROCKVILLE, MD 20850

DATE MAILED
01/27/94

AJM

MAINTENANCE FEE STATEMENT

The data shown below is from the records of the Patent and Trademark Office. If the maintenance fees and any necessary surcharges have been timely paid for the patents listed below, the notation "PAID" will appear in column 10, "status" below.

If a maintenance fee payment is defective, the reason is indicated by code in column 10, "status" below. An explanation of the codes appears on the reverse of the Maintenance Fee Statement. TIMELY CORRECTION IS REQUIRED IN ORDER TO AVOID EXPIRATION OF THE PATENT. NOTE 37 CFR 1.377. THE PAYMENT(S) WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION. IF PAYMENT OR CORRECTION IS SUBMITTED DURING THE GRACE PERIOD, A SURCHARGE IS ALSO REQUIRED. NOTE 37 CFR 1.20(k) and (l).

If the statement of small entity status is defective the reason is indicated below in column 10 for the related patent number. THE STATEMENT OF SMALL ENTITY STATUS WILL BE ENTERED UPON RECEIPT OF ACCEPTABLE CORRECTION.

ITM NBR	PATENT NUMBER	FEE CDE	FEE AMOUNT	SUR CHARGE	SERIAL NUMBER	PATENT DATE	FILE DATE	PAY YR	SML ENT	STAT
1	4,938,763	283	465	----	07/252,645	07/03/90	10/03/88	04	YES	PAID

If the "status" column for a patent number listed above does not indicate "PAID" a code or an asterisk (*) will appear in the "status" column. Where an asterisk (*) appears, the codes are set out below by the related item number. An explanation of the codes indicated in the "status" column and as set out below by the related item number appears on the reverse of the maintenance fee statement.

ITM NBR	ATTY DKT NUMBER
1	1944.014

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"FEE ADDRESS" INDICATION FORM MG 8905

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ROCKVILLE, MD 20850

PAYOR NUMBER: 000204

In the following listed application(s) or patent(s) for which the issue fee has been paid.

PATENT NUMBER	SERIAL NUMBER	PATENT DATE	U.S. FILING DATE	OUR REFERENCE
4938763	252645	03JUL90	03OCT88	MG8905.070

SIGNED X Albin J. Nelson

Typed name of person signing ALBIN J. NELSON, Reg. 28,650

Title & Corporation

(check one)

|___| Owner of record
|_X_| Owner s attorney or agent of record

Y prior fee addressee form previously submitted is hereby revoked.

3M PTO-1537

Exhibit 5

(IND SUBMISSION LETTER).

April 17, 1990

Food and Drug Administration
Document Control Section HFN-46
Park Building, Room 214
12420 Parklawn Drive
Rockville, Maryland 20857

Dear Madam/Sir:

In accordance with 21 CFR 312.23, ATRIX LABORATORIES INC., (formerly Vipont Research Laboratories, Inc.) is submitting an Investigational New Drug Application (IND) in support of a biodegradable polymer delivery system containing the antibiotic doxycycline hyclate USP for treatment of periodontitis. A pre-IND meeting was held on June 7, 1989 with the Division of Anti-Infective Drugs to discuss the general clinical plan and toxicology/pharmacology data requirements for the IND.

Periodontal disease is responsible for the loss of teeth in millions of Americans. Periodontitis, the most common destructive form of periodontal disease, is characterized by bacterial infection and inflammation, formation of periodontal pockets, and bone deterioration with subsequent loss of teeth. It is recurring, progressive, and episodic. Current treatments range from periodic cleaning, scaling, and root planing to surgery. The product that we request permission to evaluate in humans under this IND, if successful, will lead to a unique non-surgical procedure in which periodontitis can be treated with less expense, discomfort, and cosmetic concerns than the current treatment procedures. The availability of such a product to the dental professional will provide a treatment which may increase the number of people who seek and maintain professional help for this destructive dental disease.

Because of the need for and interest in a localized chemotherapeutic treatment for periodontitis, we look forward to a collaborative effort with the Food and Drug Administration in the expeditious and successful evaluation of the proposed product.

If you have any questions regarding the IND, please contact me at 303-482-5868.

Sincerely,

Elaine M. Gazdeck
Regulatory Affairs Associate

cc. P. DeSantis, HFD 521

Exhibit 6

(IND ACKNOWLEDGMENT LETTER)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

RECEIVED

MAY 1 1990

REGULATORY AFFAIRS

IND 34,690

Date April 26, 1990

Atrix Laboratories, Inc.
1625 Sharp Point Drive
Fort Collins, Colorado 80525

Attn: Elaine M. Gazdeck
Regulatory Affairs Associate

Dear Sir or Madam:

We acknowledge receipt of your Investigational New Drug Application (IND) submitted pursuant to Section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 34,690

Sponsor: Atrix Laboratories, Inc.

Name of Drug: Doxycycline Hyclate, USP

Date of Submission: April 17, 1990

Date of Receipt: April 18, 1990

Studies in humans may not be initiated until 30 days after the date of receipt shown above. If, within the 30-day waiting period, we identify deficiencies in the IND that require correction before human studies begin or that require restriction of human studies until correction, we will notify you immediately that the study may not be initiated ("clinical hold") or that certain restrictions must be placed on it. In the event of such notification, you must continue to withhold, or to restrict, such studies until you have submitted material to correct the deficiencies, and we have notified you that the material you submitted is satisfactory.

It has not been our policy to object to a sponsor, upon receipt of this acknowledgement letter, either obtaining supplies of the investigational drug or shipping it to investigators listed in the IND. However, if drug is shipped to investigators, they should be reminded that studies may not begin under the IND until 30 days after the IND receipt date or later if the IND is placed on clinical hold.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and the regulations implementing that Act (Title 21 of the Code of Federal Regulations). Those responsibilities include reporting any adverse experience associated with use of the drug that is both serious and unexpected to the FDA as soon as possible and in no event later than 10 working days after initial receipt of the information and reporting any unexpected fatal or life-threatening experience to the FDA by telephone no later than 3 working days after receipt of the information (21 CFR 312.32), and submission of annual progress reports (21 CFR 312.33).

Please forward all future communications concerning this IND in triplicate, identified by the above IND number, and addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research (HFD-160)
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this IND, please contact Jocelyn Lewis at (301) 443-3560

Sincerely yours,

Supervisory Consumer Safety Officer
Division of Medical Imaging, Surgical
and Dental Drug Products
Office of Drug Evaluation
Center for Drug Evaluation and Research

cc: Original IND - pink
HFD-160 - yellow
HFD-160/CSO - green

IND ACKNOWLEDGEMENT

Exhibit 7

(LETTER TO F.D.A. OF JULY 15, 1991)

ATRIX
LABORATORIES, INC.

July 15, 1991

Food and Drug Administration
Bureau of Drugs, HFD-160
Document Control Room 18B-03
1600 Fishers Lane
Rockville, MD 20857

Attention: Julie Rhee
Consumer Safety Officer
Medical Imaging, Surgical, and Dental Drugs

Subject: IND 34,690: VR-300 (5% Doxycycline)
Annual Report (April 26, 1990 - April 26, 1991)
Serial #001

As required by 21 CFR Section 312.33, enclosed is the first annual report for IND 34,690. Included are a summary of the clinical study completed and significant chemistry/manufacturing changes. Revisions on Specifications and Test Methods are highlighted for ease of review. No adverse experiences were reported and no one dropped out of the study.

Since a corporate decision was made to reallocate resources for this project, no clinical studies are now in progress or planned. As required by 21 CRF Section 312.45, we request that the IND be placed into inactive status by FDA. All drug product has been disposed in accordance with 21 CFR Section 312.59 from the completed clinical study.

If there are any questions concerning this information and/or request to place the IND into inactive status, please contact me.

Sincerely,

Elaine M. Gazdeck
Manager, Regulatory Affairs

P.O. BOX 20150 • FORT COLLINS, COLORADO 80522 • PHONE: (303) 482-5868

Exhibit 8

(F.D.A. LETTER OF NOVEMBER 5, 1991)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND 34,690

NOV 5 1991

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

RECEIVED

Atrix Laboratories, Inc.
2579 Midpoint Drive
Fort Collins, Colorado 80525

NOV 8 1991

REGULATORY AFFAIRS

Attention: Elaine M. Gazdeck
Manager, Regulatory Affairs

Dear Ms. Gazdek:

Please refer to your Investigational New Drug Application (IND) 34,690 submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for VR-300 (5% doxycycline hyclate).

We also refer to your request of July 15, 1991 that this IND be placed on inactive status.

This IND is now considered to be on inactive status. Please note that an IND that is inactive for 5 years or more may be terminated under 21 CFR 312.44(b)(x).

We note that there are no ongoing clinical studies and that you have properly accounted for all stocks of the drug.

If you decide in the future to resume clinical investigations under this IND, it is required that you submit a protocol amendment under 21 CFR 312.30 containing the proposed general investigational plan for the coming year and appropriate protocols. Any additional information supporting the proposed investigation should be submitted in an information amendment. We further remind you that, notwithstanding the provisions of 21 CFR 312.30, clinical investigations under an IND on inactive status may only resume 30 days after FDA receives the protocol amendment.

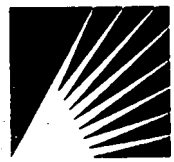
Thank you for your cooperation.

Sincerely,

Wiley A. Chambers, M.D.
Acting Director
Division of Medical Imaging,
Surgical and Dental Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Exhibit 9

(COVER LETTER TO F.D.A. OF JUNE 29, 1992)



June 29, 1992

Food and Drug Administration
Bureau of Drugs, HFD-160
Document Control Room 18B-03
5600 Fishers Lane
Rockville, MD 20857

Attention: Susan Lang, Consumer Safety Officer
Medical Imaging, Surgical and Dental Drugs

Subject: IND 34,690: Doxycycline in the ATRIGEL™ Delivery System
Request to Reactivate the IND - New Protocol Amendment
Serial #002

In accordance with 21 CFR 312.45(d), we are submitting a new protocol amendment to resume clinical investigation under this IND which had been placed under inactive status on November 5, 1991. The new protocol is a Phase II study entitled **ACS-28: A Multi-Center, Parallel Design, Single-Blind Study Comparing VR-100 (Polymer with 5% Sanguinarine Chloride), VR-302 (Polymer with 5% Doxycycline Hyclate,), VR-303 (Polymer with 10% Doxycycline Hyclate), and VR-100P (Polymer Formulation Alone), in Reducing the Clinical Signs Associated with Periodontitis.** The objective of the study is to identify the best candidate product to test further in a Phase III clinical evaluation. This same protocol is also being submitted concurrently to the sanguinarine chloride IND 32,146.

As discussed at an April 7, 1992 meeting with Division personnel, results from the Phase III split-mouth studies ACS-16 and 17 with VR-100 and VR-100P suggested that there might have been a cross-over effect. Therefore, ACS-28 is being conducted to clarify these results, and at the same time, ascertain whether the 5% and 10% doxycycline ATRIGEL™ formulations have clinical potential for treating periodontitis. The protocol incorporates FDA suggestions made at the April 7th meeting as well as certain aspects from the proposed American Dental Association Guidelines for Non-surgical Treatment of Adult Chronic Periodontitis. The product yielding the best treatment outcome from this study will proceed to Phase III clinical evaluation.

Included in this amendment are an Introduction and a Clinical Section. The Introduction explains in more detail the reasons for conducting ACS-28. The Clinical Section contains an investigational plan, protocol synopsis with rationale for the study design, patient population, and treatment regimen, and a copy of the protocol and investigator's brochure. A desk copy of this amendment is being sent to Dr. Gilkes.

2579 MIDPOINT DRIVE • FORT COLLINS, COLORADO 80525 • PHONE (303) 482-5868

Under separate cover two Information Amendments, Serial # 003 and #004, are being submitted concurrently in support of this clinical investigation. The Toxicology Information Amendment provides additional pre-clinical results for a study conducted in dogs to evaluate the drug release profile, bioactivity, and safety of the two doxycycline formulations. The Chemistry, Manufacturing, and Controls (CMC) Information Amendment explains the revisions to the CMC information for the 5% formulation and provides CMC information for the new 10% formulation.

If you have any questions regarding this amendment, please contact me at 303-482-5868.

Sincerely,

Elaine Gazdeck
Manager, Regulatory Affairs

Exhibit 10

(NDA SUBMISSION LETTER).

2579 MIDPOINT DRIVE
FORT COLLINS, CO 80525-4417
U.S.A.

PHONE: (970) 482-5868
FAX: (970) 482-9735
EMAIL: atrixlab@frii.com
http://www.atrixlabs.com

March 31, 1997

U.S. Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Park Building, Room 214
14240 Parklawn Drive
Rockville, MD 20852

Attention: Dr. Hal Blatt, Consumer Safety Officer

In accordance with 21 CFR 314, enclosed is New Drug Application (NDA) 50-751 for the ATRIDOX™ drug product. ATRIDOX™ is a topical dosage form indicated for use in treating chronic adult periodontitis.

As required by 21 CFR 314(k)(1), an archival copy of the application is included which contains the following information:

Volume 1	Application Form, Index, and Summary as required under 21 CFR 314.50(a), (b), and (c),
Volumes 2-8	Chemistry, Manufacturing, and Controls technical section as required under 21 CFR 314.50(d)(1),
Volumes 9-13	Nonclinical Pharmacology and Toxicology technical section as required under 21 CFR 314.50(d)(2),
Volumes 14-18	Human Pharmacokinetics and Bioavailability technical section as required under 21 CFR 314.50(d)(3),
Volumes 19,20	Microbiology technical section as required under 21 CFR 314.50(d)(4),
Volumes 21-74	Clinical/Statistical technical section as required under 21 CFR 314.50(d)(5) and (6),
Volumes 75-285	Case Report Forms as required under 21 CFR 314.50(f)(2), and
Volume 286	Electronic SAS data sets for integrated safety information and efficacy of Phase 3 studies ACS-34 and ACS-35.

Tabulations of case report forms as required by 314.50(f)(1) are included as follows:

Tabulations of data to support clinical investigations are included as part of each final study report. Additionally, as requested by FDA at the Pre-NDA meeting held January 7, 1997 (refer to IND 34690 Serial # 075 for Atrix meeting minutes), electronic SAS data sets of integrated safety information and efficacy data for Phase 3 clinical studies ACS-34 and ACS-35 are included (volume 286).

As required by 21 CFR 314.50(k)(2), a review copy of the application, inclusive of volumes 1 through 74 is also included. Six copies of volume 1 are provided for distribution to each reviewing discipline. Additionally, a second copy of the electronic data sets (volume 286) are included for the Statistical reviewers. As suggested by the FDA Guideline (February 1987) for Format and Content of Chemistry, Manufacturing, and Controls Section of an (NDA) Application, Section III, three additional copies of volume 5 (Samples and Methods Validation Subsection) of the application are being submitted with the CMC review copy.

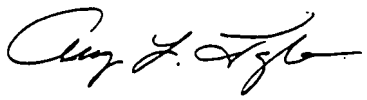
As required by 21 CFR 314.50(k)(3), a field copy containing volumes 1 through 8 of the application has been forwarded to the Denver District office. A copy of the letter of certification for this field copy is attached.

Primary stability studies are currently being conducted on three product lots manufactured at 1/10 market scale in the proposed commercial packaging. An interim report supplying data at the initial and 3 month time points is included in the CMC technical section. As discussed with FDA reviewers at the Pre-NDA meeting, additional data from the primary stability studies will be supplied in a series of amendments to the NDA as it becomes available.

Regarding user fees, Atrix is currently in the process of applying for a small business exemption.

Please contact me if you have any questions regarding the submitted information.

Sincerely,



Amy L. Taylor, Regulatory Affairs Project Leader

Exhibit 11

(F.D.A. LETTER OF APRIL 1, 1997)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 50-751

Atrix Laboratories, Inc.
Attentention: Amy L. Taylor
2579 Midpoint Drive
Fort Collins, CO 80525-4417

APR 29 1997

Dear Ms. Taylor:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Atridox (doxycyclione hyclate)

Therapeutic Classification: 3S

Date of Application: March 31, 1997

Date of Receipt: April 1, 1997

Our Reference Number: 50-751

The User Fee Payment was not received until April 7, 1997. Therefore, the application was unacceptable for filing until that date.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on June 6, 1997 in accordance with 21 CFR 314.101(a).

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Exhibit 12

(CORRESPONDENCE INDEX IND 34, 690)

ATRIGEL® Delivery System with Doxycycline Hyclate
Correspondence Index
IND 34,690

Date	Document
09/05/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate. Protocol Amendment: New Protocol AGD9705, Bioequivalence Study. Serial #083. See Binder #58.
10/17/97	Note to File: Phone call from Dr. Sue Lee, FDA Biopharmaceutics Reviewer, 301/827-2035, re: status of AGD9705 Clinical Study.
11/10/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate. Protocol Amendment: New Protocol AGD9609, Feasibility Study. Serial #084. See Binder #59.
12/04/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate. Protocol Amendment: New Protocol AGD9704, Feasibility Study. Serial #085. See Binder #60.
03/09/98	Submission of IND 34690: ATRIGEL® Delivery System with Doxycyclline Hyclate. IND Safety Report. Serial #086.
05/14/98	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate. Information Amendment: Chemistry, Manufacturing & Control. Protocol Amendment: Addition of Alternate Supplier of Doxycycline Hyclate. Serial #087.
08/24/98	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate. Annual Report. Serial #088. See Binder #61.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through 02/05/97)

Date	Description
06/06/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate, Informational Amendment: Atrix Response to FDA Meeting Minutes and Request for Clarification from FDA. Serial #079.
06/06/97	Phone conversation with Dr. Hal Blatt, FDA CSO re: response to Clinical Study Design Proposal for Adjunctive Claim (Atrix Clinical Study AGD9609) and Request for Clarification on FDA Meeting Minutes.
06/09/97	Phone call from Dr. Hal Blatt, FDA CSO re: Atrix inquiry of proposal for AGD9609.
06/19/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Protocol Amendment: New Protocol AGD9701. Serial #080. See Binder #56.
06/25/97	Fax from Dr. Hal Blatt, CSO, FDA, re: FDA Meeting minutes on NDA 50-751 on 05/20/97.
06/27/97	Phone call to Dr. John Kelsey, FDA Dental Reviewer (301/827-2035) re: response to Clinical Study Design Proposal for Adjnctive Claim (Atrix Clinical Study AGD9609).
07/01/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Minutes from CMC Teleconference. Serial #081.
07/11/97	Phone call to Dr. John Kelsey, FDA Dental Reviewer (301/827-2035) from Dr. Steve Garrett re: AGD9609 Clinical Study Proposal.
07/21/97	Fax from Dr. Hal Blatt, CSO forwarding comments from Clinical Reviewer on Submission #078 on IND34690.
08/29/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate: Annual Report. Serial #082. See Binder #57.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through 02/05/97)

Date	Description
02/03/97	Fax to Dr. Hal Blatt, CSO re: Pre-NDA Meeting Minutes.
02/04/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Reference Letter of Authorization - Block Drug Company. Serial #076.
02/05/97	Fax to Dr. Hal Blatt, CSO re: list of Atrix personnel who will be in teleconference; authorization letter to allow representatives from Block Drug.
02/05/97	Information forwarded for FDA teleconference on February 10 and question regarding electronic version of PK Clinical Study Reports.
02/28/97	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Protocol Amendment: New Protocol AGD 9607. Serial #077. See Binder #55.
04/24/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Request for Response for Study Design for AGD 9609. Protocol for New Indication. Serial #078.
04/25/97	Letter to Dr. Hal Blatt, CSO enclosing desk copies for 2 submissions forwarded to FDA in the last 10 days. (#1: NDA 50-751 submitted 04/17/97 and #2 IND 34690 submitted 04/24/97.)
05/12/97	Phone call from Dr. Hal Blatt, CSO, FDA re: summarization of the fax re: Establishment Registration Number or Central File Number for Ranbaxy.
05/14/97	Phone calls from Dr. Hal Blatt, CSO, FDA re: request for responses to the 4 month safety update for NDA 50-751 and the proposed clinical study AGD9609 that was submitted to IND 34690.
05/21/97	Breakfast meeting with Dr. Kelsey, Dr. Hyman and Dr. Srinivasan, FDA Reviewers.
06/02/97	Minutes of Meeting (ID#577) from FDA (Dr. Hal Blatt, CSO) Pre-NDA & Guidance Meeting Minutes from Pre-NDA Meeting on 01/07/97.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through)

Date	Description
01/03/97	Fax to Dr. Hal Blatt, CSO re: Submission #074: Letter of Authorization - Block Drug Company.
01/03/97	Phone call from Dr. Kelsey (FDA Medical Reviewer) to Dr. Garrett.
01/06/97	Phone call from Dr. Hal Blatt (CSO) to verify receipt of Block Authorization letter and inquire about Microbiology review.
01/08/97	Fax from Division of Dermatologic & Opthalmologic Drug Products re: information forwarded for upcoming CMC meeting.
01/08/97	Phone call from Dr. Hal Blatt (CSO) to relay requests from Microbiology reviewer for electronic file format of NDA.
01/09/97	Phone call to Dr. DeCamp (FDA Chemistry Team Leader) to request scheduling of CMC meeting.
01/13/97	Phone call to Division of New Drug Chemistry III - (301) 827-2025.
01/15/97	Phone call to Dr. John Kelsey (FDA Medical Reviewer - [301] 827-2035) to discuss case report form request for NDA.
01/17/97	Phone call to Dr. James Vidra (FDA Chemistry Reviewer) re: scheduling a CMC meeting as requested by FDA at the Pre-NDA meeting.
01/18/97	Phone call from Dr. DeCamp (FDA Chemistry Team Leader) re: scheduling of meeting to discuss CMC format & content for the NDA.
01/28/97	Phone call to Dr. Tony DeCamp (FDA Chemistry Team Leader) [301/827-2041] to discuss scheduling of CMC-NDA meeting.
01/28/97	Phone call to Dr. Tony DeCamp (FDA Chemistry Team Leader) [301/827-2041] to discuss scheduling of CMC-NDA meeting.
02/03/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Minutes from Pre-NDA Meeting. Serial #075.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through)

Date	Description
12/02/96	Submission of IND 34,690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Protocol Synopsis AGD9607. Serial #072.
12/03/96	Phone call to Dr. Jim Vidra (FDA Chemistry Reviewer) to clarify FDA request for extractables testing.
12/04/96	Phone call to Sandy Chiles to confirm Pre-NDA meeting with FDA on 01/07/96.
12/06/96	Phone call from Dr. Kelsey to Dr. Garret re: clinical study requirements for Product Application with No Retentive Material.
12/10/96	Fax to Dr. Hal Blatt, CSO re: phone correspondence with Dr. Srinivasan, Dr. Kelsey & Dr. Vidra.
12/10/96	Phone call to Dr. Hal Blatt, CSO
12/12/96	Fax to Dr. Hal Blatt, CSO re: correspondence of phone conversation with Dr. Sue Chih Lee.
12/12/96	Phone call to Biopharmceutics Reviewer Dr. Sue Chih Lee (301) 827-2084.
12/18/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Pre-NDA Meeting Materials. Serial #073.
12/19/96	Phone call from Dr. Sue Chih Lee (301) 827-2085 re: status of clinical study AGD9610 submitted in serial #071.
12/30/96	Phone call from Sandy Chiles re: receipt of Serial #073.
01/03/97	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Reference Letter of Authorization - Block Drug Company. Serial #074.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through)

Date	Description
12/02/96	Submission of IND 34,690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Protocol Synopsis AGD9607. Serial #072.
12/03/96	Phone call to Dr. Jim Vidra (FDA Chemistry Reviewer) to clarify FDA request for extractables testing.
12/04/96	Phone call to Sandy Chiles to confirm Pre-NDA meeting with FDA on 01/07/96.
12/06/96	Phone call from Dr. Kelsey to Dr. Garret re: clinical study requirements for Product Application with No Retentive Material.
12/10/96	Fax to Dr. Hal Blatt, CSO re: phone correspondence with Dr. Srinivasan, Dr. Kelsey & Dr. Vidra.
12/10/96	Phone call to Dr. Hal Blatt, CSO
12/12/96	Fax to Dr. Hal Blatt, CSO re: correspondence of phone conversation with Dr. Sue Chih Lee.
12/12/96	Phone call to Biopharmceutics Reviewer Dr. Sue Chih Lee (301) 827-2084.
12/18/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Pre-NDA Meeting Materials. Serial #073.
12/19/96	Phone call from Dr. Sue Chih Lee (301) 827-2085 re: status of clinical study AGD9610 submitted in serial #071.
12/30/96	Phone call from Sandy Chiles re: receipt of Serial #073.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through)

Date	Description
11/13/96	Fax to Dr. Hal Blatt (CSO) and Sandy Chiles re: confirmation that second request from Atrix for a Pre-NDA Meeting had not been received by FDA.
11/18/96	IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate, Briefing Materials for Pre-NDA Meeting. Ten copies of briefing materials requested by Sandy Chiles.
11/19/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Protocol Amendment: New Protocol AGD9610. Serial #071. See Binder #54.
11/20/96	Phone call to Dr. Hal Blatt (CSO) re: previous correspondence.
11/20/96	Phone call from Susan Duke to Dr. Srinivasan (301/827-2077) to discuss question in fax correspondence of October 22, 1996.
11/20/96	Phone call to Sandy Chiles - FDA Meeting Coordinator.
11/20/96	Phone call from Dr. Steven Garrett to Dr. John V. Kelsey (301/827-0978) to discuss question in fax correspondence of October 22, 1996.
11/21/96	Phone call from Susan Duke to Dr. R. Srinivasan (FDA Statistical Reviewer) to discuss question in fax correspondence of 10/22/96 and follow-up correspondence of 10/31/96 and 11/6/96 re: site vs. Subject bases analysis for peridontal clinical studies.
11/21/96	Phone conversations with Sandy Chiles, FDA Meeting Coordinator, to dsicuss scheduling of Pre-NDA meeting.
11/22/96	Voice mail from Dr. Hal Blatt (CSO) re: receipt of fax correspondence 11/13/96 concerning Pre-NDA meeting and telephone correspondence to Dr. Kelsey & Dr. Srinivasan.
11/27/96	Phone call from Dr. John Kelsey (FDA Medical Reviewer) to Dr. Steve Garrett re: clinical study requirements for no retentive material claim.

ATRIGEL® Delivery System With Doxycycline Hyclate
Correspondence Index
IND 34,690
(01/11/96 through)

Date	Description
10/08/96	Phone conversation with Dr. Hal Blatt (CSO) re: FDA responses to our October 1 teleconference on sample size calculations for AGD9603 clinical study and September 11 teleconference on the proposal to modify blending procedure for constitution of the VR-303-ABS product.
10/09/96	Fax to Dr. Hal Blatt (CSO) re: additional information to be forwarded to Dr. Harkin, Dr. Hyman and Dr. Kelsey that will help in defining appropriate statistical parameters for AGD9603.
10/09/96	Phone conversation with Sandy Chiles re: teleconference to discuss sample size calculations for the AGD9603 clinical study.
10/22/96	Fax to Dr. Hal Blatt (CSO) re: review of clinical trial options proposed in teleconference of October 10, 1996.
10/25/96	Phone call to Dr. Hal Blatt (CSO) to confirm receipt of October 22, 1996, FAX with two additional questions.
10/30/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Protocol Amendment: Amended Protocol AGD9603; Additional Information: Atrix Teleconference Minutes. Serial #070. See Binder #53.
10/31/96	Fax to Dr. Hal Blatt (CSO) re: response to FDA phone call of October 29, 1996, re: clarification of information contained in item one of Atrix correspondence of October 22, 1996.
11/05/96	Phone call from Dr. Hal Blatt (CSO) to follow up on fax correspondence of October 22 and 31, 1996.
11/06/96	Fax to Dr. Hal Blatt (CSO) re: response to Dr. Srinivasan's request for written copy of reference from AAP.
11/08/96	Phone call to Sandy Chiles.
11/12/96	Fax to Sandy Chiles re: Pre-NDA Meeting Request previously submitted in September along with a proposed agenda.

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Date	Description
08/16/96	Teleconference with FDA to discuss sample size calculation for AGD9603.
08/30/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Annual Report, Final Study Report Atrix Clinical Study (ACS) 32. Serial #066. See Binder 50 (1-4).
09/03/96	Phone call to Dr. James Vidra (Chemistry Reviewer) to discuss new supplier of USP doxycycline hyclate and scheduling of teleconference to discuss CMC issues for the pre-NDA meeting. A follow up phone call was also placed to Dr. Hal Blatt (CSO) to notify him of the discussion with Dr. Vidra. Dr. Blatt was not available so the message was left on his voice mail.
09/17/96	Summary information re: the Proposal for Modification to Blending Procedure for Constitution of the ATRIGEL® Delivery System with Doxycycline Hyclate Drug Product. Initial proposal submitted in Serial #063; Experimental data re: ruggedness of blending submitted in the Annual Report in Serial #066.
09/17/96	Phone call from Dr. Hal Blatt to note who the biopharmaceutics review for our project is.
09/18/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Protocol Amendment: Amended Protocol AGD9603; Reference authorization letter for Sarah Grossi, DDS, MS. Serial #067.
09/20/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Information Amendment: Minutes from Teleconference with FDA to Discuss CMC Amendment - Serial #063. Serial #068.
09/23/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Request for Pre-NDA Meeting. Serial #069. See Binder #52.
09/23/96	Fax to Dr. Hal Blatt forwarding issues re: sample size calculations for AGD9603 to be passed on to Dr. Harkin.

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Date	Description
07/08/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Chemistry and Manufacturing Controls, Proposal for Stability Package for NDA Filing, Proposal for Modification to Blending Procedure for Constitution of the ATRIGEL® Delivery System with Doxycycline Hyclate Product. Serial #063.
07/15/96	Statistical basis reference material for meeting with FDA on July 18, 1996 faxed to Dr. Hal Blatt.
07/19/96	Fax regarding points of clarification from meeting with FDA on July 18, 1996 on AGD9603 clinical study protocol.
07/25/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Informational Amendment: Minutes from meeting with FDA to discuss Atrix Clinical Study AGD9603 and requested follow up information. Serial #064. See Binder #48.
08/01/96	Faxed memo to Dr. Hal Blatt regarding minutes from 07/31/96 teleconference with FDA, requesting names and titles of additional participants in teleconference, calculations for subject numbers, status of protocol amendment submission.
08/07/96	Fax from Dr. Hal Blatt sending FDA's Data Validation and Statistical Evaluation per Atrix's request.
08/08/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Protocol Amendment: New Protocol AGD9603. Serial #065. See Binder #49.
08/12/96	Memo to file re: telephone call from Sandy Chiles discussing setting up teleconference tentatively for Friday, August 16.
08/13/96	Telephone call to Dr. Hal Blatt re: fax sent pertaining to sample size calculation for AGD9603.
08/13/96	Fax to Dr. Hal Blatt requesting citation for power program by M. Borenstein and J. Cohen in preparation for teleconference on Friday, 08/16/96.

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Date	Description
05/24/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Briefing Materials for Requested Meeting, Protocol AGD9603. Serial #060.
05/24/96	Telephone calls to Sandy Chiles to determine status of requested meetings.
05/31/96	Telephone calls to Dr. Blatt, CSO, to discuss possibility of July 8th meeting.
06/03/96	Telephone calls from Sandy Chiles on status of requested meetings.
06/04/96	Telephone calls to Dr. Blatt, CSO, to confirm understanding of meetings requested.
06/06/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate Reference Authorization Letter for Heska Corporation. Serial #061.
06/12/96	Telephone call from Sandy Chiles, division meeting coordinator, regarding schedule of our "working meeting" to discuss the protocol design of AGD-9603.
06/19/96	Telephone calls (June 18/June 19) with Dr. Hal Blatt, CSO regarding "working meeting" to discuss design of clinical study AGD-9603 and appropriate timing for a pre-NDA meeting.
06/19/96	Telephone calls with Sandy Chiles regarding the scheduling of the "working meeting" to discuss design of clinical study AGD-9603 and the pre-NDA meeting.
06/21/96	Submission of IND34690: ATRIGEL® Delivery System with Doxycycline Hyclate IND Safety Report. Serial #062.
06/26/96	Telephone call from Sandy Chiles regarding confirmation of July 18 for the "Working Meeting" to discuss design of clinical study AGD9603 and scheduling of the Pre-NDA Meeting.

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Date	Description
03/22/96	Telephone call from Dr. Kelsey regarding teleconference meeting minutes with Dr. Blatt on March 22; Dr. Kelsey's meeting with Drs. Hyman and Wilkens on March 29.
03/25/96	Telephone call from Dr. Hal Blatt, FDA CSO regarding submitting a copy of the 1995 annual report to Dr. Dunn for her review.
03/27/96	Submission of IND 34690: ATRIGEL™ Delivery System with Doxycycline Hyclate Response to FDA Request. Serial #057.
04/03/96	Note to file for IND. Telephone call from Dr. J. Kelsey regarding supplemental clinical study.
04/08/96	Note to file for IND. Telephone call to Dr. Hal Blatt, FDA CSO, to obtain additional clarification of Dr. Wilkens' recommendations on an additional clinical study.
04/10/96	Submission of IND 34690: ATRIGEL™ Delivery System with Doxycycline Hyclate Request for Meeting. Serial #058.
04/15/96	Telephone call to Dr. Blatt, FDA CSO, to determine progress on arranging a meeting to discuss design of AGD-9603.
05/03/96	Submission of IND 34690: ATRIGEL® Delivery System with Doxycycline Hyclate Request for Pre-NDA Meeting. Serial #059. See Binder #47.
05/07/96	Telephone calls to Sandy Chiles, FDA Meeting Coordinator, to determine date of meeting requested April 10, 1996.
05/15/96	Telephone call to Dr. Hal Blatt, CSO, regarding status of pre-NDA meeting request submitted May 3, 1996.
05/22/96	Telephone call to Sandy Chiles, Meeting Coordinator, to obtain status on both meeting requests.
05/22/96	Facsimile to Sandy Chiles re: letter requesting pre-NDA meeting dated 05/03/96.

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Date	Description
01/11/96	Telephone call to Dr. Roy Blay, FDA CSO, to reschedule meeting of January 10th.
02/01/96	Submitted additional Copies of Meeting Materials. Serial #054.
02/08/96	Note to file for IND. Rescheduling of FDA meeting.
02/09/96	Telephone call of February 9, 1996 from Sandy Chiles (Ed Wilkins' CSO) regarding meeting schedule to discuss AGD-9603 (ACS-39) clinical study protocol.
02/20/96	Contact with FDA regarding rescheduling meeting of March 4, 1996
02/22/96	Contact with Dr. Fred Hyman, Dental Reviewer, regarding rescheduling meeting for March 4th.
02/29/96	Request for Teleconference. Serial #055. (See binder #46).
03/06/96	Fax to Sandy Chiles - HFD 540. 02/29/96 cover letter requesting teleconference.
03/06/96	Telephone conversation with Dr. Hal Blatt, FDA CSO, regarding Atrix submission of 2/29/96 and request for teleconference.
03/07/96	Telephone calls to and from Dr. Hal Blatt, FDA CSO, to arrange teleconference.
03/08/96	Fax to Dr. Howard Blatt regarding March 15th teleconference.
03/11/96	Fax to Dr. Howard Blatt regarding teleconference to be held March 15.
03/21/96	Telephone call to and from Dr. Hal Blatt, FDA CSO, regarding minutes of teleconference and FDA call scheduled for March 29th.
03/22/96	Submission of IND 34690: ATRIGEL™ Delivery System with Doxycycline Hyclate Minutes of March 15, 1996 Teleconference. Serial #056.

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Date	Description
12/15/95	Telephone call from Sandy Cook, Division of Anti-inflammatory, Analgesic and Dental Drugs regarding meeting date to discuss issue of modified investigational plan.
12/20/95	Telephone call to Dr. Roy Blay, FDA CSO, to confirm meeting scheduled for January 10th.

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Date	Description
9/20/95	Submission of IND - New Protocol Amendment: ACS-38. Serial #050. See Binder #44.
10/11/95	Telephone call to Dr. Roy Blay, Dental CSO, to discuss the Division's reorganization and status of meeting request submitted 9/15/95 (Serial #050) pertaining to a modified investigational plan.
10/19/95	Follow-up with Roy Blay, CSO, to determine status of meeting request regarding modified investigational plan.
10/30/95	Telephone call to Roy Blay, FDA CSO, to determine his progress on contacting Dr. Gilkes relative to our meeting request of 9/15/95.
11/01/95	Submission of IND - Protocol Amendments 1 and 2: ACS-38. Serial #051. See Binder #45.
11/07/95	Telephone call from Dr. Gilkes, FDA dental reviewer, to discuss his review of our modified investigational plan submitted 9/15/95 in Serial #050.
11/13/95	Telephone call to Dr. Clarence Gilkes to further discuss the proposed investigational plan to support non-removal of the product at 7 days.
11/15/95	Telephone call from Dr. Roy Blay, FDA CSO, Division of Anti-Inflammatory, Analgesic and Dental Drugs.
11/17/95	Submission of IND - Request for meeting. Serial #052.
11/28/95	Telephone call to Dr. Roy Blay, FDA CSO, to determine status of meeting requested with Dr. Weintraub, and to discuss plans for a Pre-NDA meeting.
11/28/95	Submission of IND - Request for Pre-NDA Meeting. Serial #053.
12/06/95	Telephone call to and from Dr. Blay, FDA CSO, regarding status of determining meeting date with Dr. Weintraub.

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7/27/95	Submission of IND - Safety Report. Serial #046.
8/01/95	Telephone call to Santford Williams, FDA CSO, to determine status of response to ACS-29 design inquiry.
8/04/95	Submission of IND - Response to Chemist's Comments 7/13/95 Regarding Proposal to Add Test for Uniformity of Constitution. Serial #047. See Binder 42.
8/07/95	Telecon with Dr. Jim Cheever, FDA CSO Supervisor, regarding telefax of June 22nd concerning need for control arm in ACS-29.
8/16/95	Telephone call to Santford Williams, FDA CSO, to follow-up on submission serial #047 of 8/04/95 pertaining to test for uniformity of constitution.
8/24/95	Telephone call to Santford Williams, FDA CSO, to determine status of submission regarding Test for Uniformity of Constitution and advise him of upcoming meeting request.
9/06/95	Submission of IND - Annual Report. Serial #048. See Binder #43.
9/13/95	Telephone call to Santford Williams, FDA CSO, regarding status of review of test of uniformity of constitution comments submitted August 4, 1995.
9/15/95	Submission of IND - Request for Meeting - Revise of Clinical Investigational Plan and Proposed Modification. Serial #050.
9/18/95	Fax from J. Santford Williams, FDA CSO, regarding Serial #047, Draft Chemist's Comments.
9/18/95	Telephone call to Santford Williams, FDA CSO, to inform him of submission of new investigational plan and meeting request, and to clarify draft comments from the chemistry reviewer on the submission regarding testing for uniformity of constitution.
9/19/95	Telephone call to Bonnie Dunn, FDA Chemistry Reviewer, to clarify draft comments from the chemistry reviewer on the submission regarding testing for uniformity of constitution.

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Date	Description
5/16/95	Telephone call from John Hunt, FDA Biopharmaceutics, in response to information sent May 15 regarding ACS-29.
5/17/95	Telephone call from John Hunt, FDA Biopharmaceutics, to discuss requirements for pK studies for topical products.
5/24/95	Submission of IND - Response to FDA Chemistry Reviewer's Comments; Manufacturing Change. Serial #043. (See binder #41).
6/14/95	Submission of IND - Clinical Protocol Amendment: New Investigator for ACS-35. Serial #044.
6/15/95	Telephone call to John Hunt, FDA Biopharmaceutics, to further clarify comments from his 5/17/95 telecon.
6/20/95	Submission of IND - Proposal to Add Uniformity of Constitution Test of Product Specification; Request for Teleconference. Serial #045.
6/26/95	Telephone call to Santford Williams, FDA CSO, to obtain status of tier testing telecon and fax regarding design of PK study ACS-29.
7/05/95	Telephone call to Santford Williams, FDA CSO, to ascertain status of tier testing proposal and ACS-29 design question.
7/12/95	Telephone contacts with Santford Williams, FDA CSO, regarding status of tier testing proposal review and ACS-29 clarification of study design.
7/13/95	Draft Comments Regarding Chemistry Reviewer Comments on Tier Testing Proposal; Bonnie Dunn.
7/20/95	Telephone call to Santford Williams, FDA CSO, to discuss status of response to Dr. Dunn's comments on tier testing proposal, conversation with Dr. Gilkes regarding adding Dr. Bogle's center to ACS-35, and resolution of the design issue for ACS-29.
7/26/95	Telephone call to Santford Williams, FDA CSO, to determine status of his contacts with Jim Cheever and the review statistician.

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2/15/95	Telephone call to John Hunt, FDA Biopharmaceutics, to determine status of ACS-29 review and Guideline for Pharmacokinetic Studies for Drugs to Treat Periodontal Disease.
2/16/95	Telephone call to David Bailey, FDA Pharm/Tox Reviewer, to determine status of July 18, 1994 response to Pharm/Tox questions.
3/03/95	Telephone call from Dr. Carolyn Tylenda, CDRH, regarding the response of 2/1/95 to the questions FDA asked pertaining to the Progress Report.
3/08/95	Submission of IND - Protocol Amendment #1: Microbiological Study ACS-33. Serial #039. (See Binder #40).
3/22/95	Submission of IND - Response to Pharm/Tox Questions, Serial #27, July 18, 1994. Serial #40.
3/24/95	Telephone call to Santford Williams regarding submission of 3/22/94, Serial #40.
3/24/95	Telephone call to John Hunt, FDA biopharmaceutics reviewer, regarding review of ACS-29 (pK study) protocol.
3/29/95	Telephone call to Jim Cheever, Supervisor CSO, FDA Division of Medical Imaging, Surgical and Dental Drugs.
3/31/95	Submission of IND - Protocol Amendment: New Investigator. Serial #41.
4/20/95	Telephone call to John Hunt, FDA Biopharm reviewer, regarding ACS-29 protocol.
5/02/95	Submission of IND - Safety Report. Serial #042.
5/12/95	Telephone call to Santford Williams, FDA CSO.
5/09/95	Telephone call to John Hunt, Biopharmaceutics reviewer. Followed by a Federal Express Package sent to replace fax.

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Date	Description
12/12/94	Telephone call from Santford Williams, FDA CSO, in response to my phone call to Jim Cheever earlier that morning.
12/14/94	Fax sent to Santford Williams - Telephone conversations regarding requirement for person collecting adverse event information in Phase III studies to be blind to treatments.
12/15/94	Telephone call from Dr. Jim Cheever, Supervisory CSO, in response to fax sent 12/14/94 to Santford Williams, CSO.
12/20/94	Telephone call from Jim Cheever, FDA CSO Supervisor, regarding fax sent 12/14 on the use of an AE recorder blind to patient treatment in Phase III studies.
12/22/94	Telephone call from Dr. Jim Cheever, FDA CSO supervisor, concerning whether the person collecting AE's in the Phase III studies needed to be blind to patient treatments.
12/22/94	Submission of IND - Information Amendment: Chemistry, Manufacturing and Controls for VR-300-P (Vehicle) Control. Serial #037. (See Binder #38).
1/05/95	Submission of IND - Protocol Amendment #1: Protocols ACS-34 and ACS-35. Serial #038. (See Binder #39).
1/11/95	Telephone call to Santford Williams, FDA CSO, to determine status review of several submissions.
1/11/95	Fax received from Santford Williams, FDA CSO, draft comments of the teleconference meeting minutes.
1/17/95	Letter from Santford Williams, FDA CSO, comments from the review of IND submission of 10/5/94 and FDA letter of 8/1/94.
1/19/95	Telephone call from Jim Cheever, FDA Supervisor CSO, concerning ACS-34 and 35 protocol comments.

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10/20/94	Submission of IND New Protocol Amendment: ACS-29 and ACS-32. Serial #034. (See Binder 35).
10/26/94	Memorandum of Telephone Conversation between Frances Mielach, Ph.D., for Atrix and Santford Williams, CSO, FDA regarding Amendment #035.
11/03/94	Submission of IND - Request for Teleconference. Serial #035. (See Binder 36).
11/10/94	Telephone call between Frances Mielach for Atrix and Santford Williams. FDA. Conversation regarding Atrix teleconference with FDA.
11/14/94	Telephone call between Frances Mielach for Atrix and Santford Williams, FDA. Conversation regarding Atrix teleconference with FDA. Conversation at 8:00 a.m.
11/14/94	Telephone call between Frances Mielach for Atrix and Santford Williams, FDA. Conversation regarding Atrix teleconference with FDA. Conversation at 10:30 a.m.
11/18/94	Memorandum of Telephone Conversation between Frances Mielach, Ph.D., for Atrix and Santford Williams, CSO, FDA regarding Amendment #035.
11/22/94	Memorandum of Telephone Conversation between Frances Mielach, Ph.D., for Atrix and Santford Williams, CSO, FDA regarding Amendment #035.
11/23/94	Teleconference with Jim Cheever and Santford Williams to discuss issues outlined in submission of November 3, 1994, Serial #035.
12/01/94	Telephone call to Santford Williams, FDA CSO, to determine status of fax pertaining to CMC questions.
12/02/94	Submission of Teleconference Minutes, Serial #036. (See Binder #37)
12/07/94	Telephone call to Santford Williams, FDA CSO, to determine status of protocol comments and CMC comments to be faxed to Atrix.

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Date	Description
8/16/94	Telephone call to Santford Williams, FDA CSO, to discuss the possibility of arranging a meeting after the submission of new phase III protocols.
8/31/94	Annual Report; June 30, 1993 to June 30, 1994. Serial #030. (See Binder 31).
9/02/94	Telephone call to Santford Williams, FDA CSO, to determine status of Tox/Pharm amendment submitted 7/18/94 and ACS-33 protocol submitted 7/28/94.
9/13/94	Telephone call to Santford Williams, FDA CSO, to determine status of review of ACS-33 protocol and 7/18/94 Pharm/tox amendment.
9/13/94	Telephone call from Santford Williams, FDA CSO regarding ACS-33 protocol.
9/20/94	Call to Santford Williams, FDA CSO, to ascertain progress on review of ACS-33.
9/21/94	Submission of IND - New Protocol Amendment and Meeting Request. Serial #031. (See Binder 32).
10/04/94	Telephone call to Santford Williams, FDA CSO, to discuss the status of the review of ACS-33 and to determine if the suggested target date of November 1, 1994 for a meeting is feasible.
10/05/94	Call from Santford Williams. FDA CSO, regarding status of comments for ACS-33 and meeting date.
10/05/94	Submission of IND - Response to FDA Chemistry Reviewer's Comments. Serial #032. (See Binder 33).
10/14/94	Submission of IND Clinical Information Amendment: ACS-28 Final Report. Serial #033. (See Binder 34, 3 volumes).
10/18/94	Memorandum of Telephone Conversation between Frances Mielach, Ph.D., for Atrix and Santford Williams, CSO, FDA regarding Amendment #035.

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7/19/94	Received faxed Letter of the completed review of IND Atrigel Delivery System, Study ACS-28. Also referred to submission dated April 21, 1994, and the meeting between Atrix representatives and the FDA on February 18, 1994.
7/20/94	Telephone call to Santford Williams to determine status of third letter we will be receiving regarding ACS-31 protocol design.
7/21/94	Telephone call form Jim Cheever, FDA CSO Supervisor, regarding our call to Dr. Love.
7/22/94	Call from Jim Cheever, FDA CSO Supervisor, to advise of status of third letter.
7/25/94	Received original copy of letter which was faxed on 7/19/94. Completed review of IND Atrigel Delivery System, Study ACS-28 along with comments of submission dated April 21, 1994, and the meeting between Atrix representatives and the FDA on February 18, 1994.
7/25/94	Received Fax of Draft Comments from Jim Cheever, FDA CSO Supervisor.
7/28/94	Submission of New Protocol: ACS-33, Serial #028. (See Binder 30).
7/28/94	Receipt of 7/25/94 draft comments and plans for FDA meeting.
8/01/94	Receipt of original letter referring to IND Submission of January 6, (#017), January 17, (#019), and January 26, 1994, (#020).
8/02/94	Telephone call to Santford Williams, FDA CSO, to discuss status of official version of 7/25/94 letter and subsequent Atrix plans.
8/04/95	Submission of IND Safety Report, Serial #029.
8/11/94	Telephone call to Santford Williams, FDA CSO, to discuss status of official version of 7/25/94 letter.
8/11/94	Received official letter of reference to submission of April 21, 1994.

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Date	Description
6/03/94	Telephone call to Santford Williams to ascertain status on microbiology review of 1/17/94 CMC amendment and review of 2/18/94 meeting minutes.
6/08/94	Submission of follow-up letter to Serial #024 Submitted April 21, 1994, Serial #025 (See Binder 27).
6/14/94	Telephone call to Jim Cheever, Supervisory CSO, to determine status of 6/7/94 letter which asked for his assistance in review of 4/21/94 submission.
6/22/94	Submission of Clinical Protocol Amendment: Updated Investigator List for Study ACS-30, Serial # 026, (See Binder 28).
6/22/94	Telephone call from John Cheever, Supervisory CSO, to convey status of review of April 21, 1994 submission.
6/29/94	Telephone call to Jim Cheever, Supervisory CSO, to determine status of letters being prepared by Dr. Love in response to April 21, 1994 submission.
7/05/94	Telephone call to Jim Cheever, Supervisory CSO, to determine status on three letters which are being prepared in response to 4/21/94 submission.
7/07/94	Telephone call from Jim Cheever, FDA Supervisory CSO, to clarify certain issues pertaining to protocol outline for proposed ACS-31 study.
7/11/94	Letter from Patricia Love, M.D. regarding IND submitted for Doxycycline Hyclate, the meeting held on February 18, 1994, discussing study data from ACS-28, and the meeting minutes submitted March 21, 1994.
7/13/94	Telephone call to Jim Cheever, Supervisory CSO, to ascertain status on two remaining FDA letters in response to 4/21/94 submission.
7/18/94	Response to FDA Reviewing Pharmacologist's Comments submission, Serial #027. See Binder 29.
7/18/94	Call to Jim Cheever, FDA CSO Supervisor, to determine status of two letters to be faxed to Atrix.

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Date	Description
4/15/94	Telephone call to Julie Rhee, CSO, to verify submission Serial # 023 was received.
4/21/94	Submission of Meeting Request in Regards to the Follow-up to February 18, 1994 Meeting, Serial #024 (See Binder 26).
4/22/94	Telephone call to Julie Rhee, CSO, to verify submission Serial #023 was received.
4/25/94	Telephone call to Julie Rhee, CSO, pertaining to the submission of April 21, 1994 (acceptability of ACS-28/inclusion of untreated control in ACS-31).
5/02/94	Telephone discussion with John Hunt, FDA Biopharmaceutics, to discuss draft guidelines for pharmacokinetic study requirements for dental therapeutic drug products.
5/03/94	Telephone call to Julie Rhee, FDA CSO, to determine status of review of 4/21/94 submission and FDA questions on 2/18/94 meeting minutes.
5/09/94	Telephone call to Santford Williams to ascertain status of 4/21/94 meeting request.
5/09/94	Telephone call to Julie Rhee, FDA CSO, to discuss status of 4/21/94 meeting request and position paper.
5/10/94	Telephone call from Santford Williams, FDA CSO, on status of 4/21/94 meeting request.
5/17/94	Telephone call to Santford Williams, FDA CSO, regarding status of 4/21/94 meeting request.
5/24/94	Telephone call from Stanford Williams, FDA CSO, replying to inquiry on CANDA interviews and status of 4/21/94 submission.
6/02/94	Telephone call to Santford Williams, FDA CSO, to ascertain if letter responding to 4/21/94 submission had been sent.

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Date	Description
2/25/94	Follow-up letter to February 18, 1994 Meeting sent to Julie Rhee, Serial #021
2/25/94	Julie Rhee faxed official written comments of microbiology and pharmacology/toxicology reviews which were summarized at 2/18/94 meeting.
3/03/94	Telephone call from Julie Rhee, CSO. Acknowledged receipt of letter requesting decision on the vehicle control for ACS-31 and the inquiry about CANDA discussions.
3/09/94	Telephone call to Julie Rhee, CSO, regarding Vehicle Control in ACS-31.
3/18/94	Telephone call from Mr. Hein, FDA Tox/pharm reviewer in regards to the final submission of study reports on ATS-50 and ATS-53.
3/18/94	Telephone call from Julie Rhee, CSO, regarding the vehicle control in ACS-31, the Division's thoughts on a CANDA for the NDA, and the status of IND 32,146.
3/21/94	Submission of Meeting Minutes from February 18, 1994, Serial #022 (See Binder 24).
3/21/94	Telephone calls from Dr. Gilkes, FDA Medical Reviewer, in response to our February 25, 1994 letter.
3/24/94	Telephone call to Julie Rhee, CSO, to arrange telephone call between Dr. Polson and Dr. Gilkes.
3/28/94	Teleconference with Dr. Love, Dr. Gilkes, Julie Rhee concerning study design issues for ACS-31.
3/30/94	Telephone call from John Hunt, FDA biopharmaceutics reviewer, regarding ACS-29 (pK study) protocol.
4/11/94	Submission of Updated Investigator List Who Will Be Conducting Study ACS-30, Serial #023 (See Binder 25).

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Date	Description
1/05/94	Telephone call from Julie Rhee to advise Atrix of proposed meeting date for discussion of ACS-28 results and Phase III plans and study design.
1/06/94	Meeting materials for February 3, 1994 meeting with FDA; Serial #017 (See Binder #21).
1/07/94	Revisions to Meeting Materials for February 3, 1994 meeting; Serial #018.
1/11/94	Telephone call to Julie Rhee, CSO, regarding the February 3rd meeting.
1/13/94	Additional meeting materials sent for the February 18, 1994 meeting with FDA - Desk Copies.
1/13/94	Telephone call from Julie Rhee regarding scheduling of FDA meeting.
1/17/94	Chemistry, Manufacturing and Controls Amendment; Serial #019 (See Binder 22).
1/26/94	Additional meeting materials, ACS-29 and ACS-33 protocols, sent to Julie Rhee. Serial #20 (See Binder 23).
1/26/94	Fax of protocol synopses for studies ACS-29 and ACS-33 sent to Julie Rhee.
2/4/94	Telephone call from Norman See, FDA Pharmacological Reviewer, regarding status of submission of preclinical studies ATS-50 and ATS-53.
2/10/94	Telephone calls from Norman See, FDA pharmacology reviewer, and telephone call to Julie Rhee, FDA CSO.
2/14/94	Telephone call to Julie Rhee, CSO regarding meeting agenda for February 18th meeting.
2/15/94	Telephone call from Julie Rhee, CSO regarding samples and mixing machines for the February 18, 1994 meeting.
2/17/94	Telephone call to Julie Rhee, CSO regarding the hand carried copy of the Chemistry, Manufacturing and Controls Amendment.

Correspondence Index
IND 34,690
(04/28/89 through)

Date	Description
07/19/93	Telephone calls on July 19, 1993 to Mr. Oscar Riggleman, FDA Chemistry Reviewer, Division of Medical Imaging, Surgical and Dental Drugs, to clarify stability issues pertaining to accelerated data and selection of appropriate environmental conditions.
08/30/93	Annual Report; June 30, 1992 - June 30, 1993. Serial #012. (See Binder #16).
10/13/93	Meeting request submission of 10% Doxycycline Hyclate in the ATRIGEL™ Delivery System. Serial #012. (See Binder #17).
10/15/93	Telephone call to Julie Rhee, FDA CSO, on October 15, 1993 pertaining to meeting request submitted October 13, 1993.
10/18/93	Telephone call on October 18, 1993 from Dr. Clarence Gilkes, FDA Dental Reviewer, pertaining to our meeting request submitted October 13, 1993.
11/10/93	Telephone call on November 10, 1993 to Oscar Rigglemen concerning manufacture and labeling of VR-303 based on doxycycline content in bulk drug, i.e. doxycycline hyclate USP.
11/17/93	Telephone call from Julie Rhee, FDA Consumer Safety Officer concerning the Atrix meeting request of October 13, 1993.
11/19/93	Telephone call to Dr. Gilkes, FDA Dental Reviewer, regarding meeting request of October 13, 1993.
11/24/93	Protocol Amendment #1: Protocol ACS-30; Serial #014 (See Binder #18).
12/06/93	6 month report, pre-meeting materials: Further information for requested meeting; Serial #015 (See Binder #19).
12/10/93	Telephone call to Dr. Gilkes to determine if he had received desk copy of pre-meeting materials sent December 6, 1993 and status of meeting request.
12/17/93	General Correspondence submitted by John Urheim; Serial #016 (See Binder #20).

Correspondence Index
IND 34,690
(04/28/89 through)

Date	Description
06/29/92	Information Amendment: Chemistry, Manufacturing and Controls. Serial #004 (See Binders 10-11).
08/26/92	Protocol Amendment #1: Protocol ACS-28. Serial #005 (See Binder 12).
11/10/92	Telephone call to Oscar Riggleman, FDA Chemistry Reviewer, to discuss addition of sterile water as a processing aid to VR-303 formulation.
11/11/92	Protocol Amendment #2: Protocol ACS-28. Serial #006 (See Binder 13).
03/16/93	IND Safety Report. Control No. 93-1-V303. Serial #007.
04/01/93	Protocol Amendment #3: Protocol ACS-28. Serial #008. (See Binder 14).
04/06/93	A desk copy of Serial #002, submitted to IND 34,690 on June 29, 1992, was sent to Julie Rhee per her request. (Note: This submission was not assigned a Serial # and a copy of the information that was sent can be found in Binder 8.)
05/03/93	Telephone call from Julie Rhee, CSO, regarding April 1, 1993 submission, Serial #008. FAX from Julie Rhee with written comments.
05/07/93	Meeting Request to Discuss Preliminary Results from Clinical Study ACS-28 and Proposed Phase III Protocol. Serial #009.
05/07/93	Telephone conversation with Julie Rhee, FDA, on May 7 regarding meeting request after submission of ACS-28 preliminary 2 month data.
06/08/93	Response to 05/03/93 FAX from Julie Rhee, Serial #010.
06/18/93	Letter from Paula Botstein acknowledging reactivation of IND 34,690 as of June 30, 1992.
07/07/93	New Protocol Amendment: Protocol ACS-30. Serial #011. (See Binder 15).

Correspondence Index
IND 34,690
(04/28/89 through)

Date	Description
04/18/89	Letter to Patricia DeSantis requesting a pre-IND meeting (See Binder #1).
06/07/89	Minutes from pre-IND meeting with FDA Anti-Infective Review Division.
06/08/89; 06/09/89	Telephone call from Dr. Browder regarding the dog irritation study design.
08/31/89	Telephone call to Dr. Browder regarding design of the dog gingival irritation study.
04/17/90	Submitted original IND; Serial #000 (See Binders #2-6).
04/25/90	Telephone call from Mr. Vann Sickler, Consumer Safety Officer, Anti-Infective Drugs Division, FDA.
04/26/90	Letter from FDA acknowledging receipt of IND.
11/13/90	Telephone call to Jocelyn Lewis to determine status of comments.
07/15/91	Annual Report; Serial #001 (See Binder #7).
11/08/91	Letter from FDA, Wiley A. Chambers, M.D., Acting Director, informing ATRIX of acceptance of its request for inactive status.
03/31/92	Telephone call to Mr. Riggleman, FDA Chemistry Reviewer, to discuss doxycycline hyclate relative purity of the bulk material and subsequent formulations and label claims.
04/08/92	Telephone call to Mr. Riggleman, FDA Chemistry Reviewer, from Paul Reinhart to review allowable levels of impurities in doxycycline hyclate found in the bulk drug as well as impurities formed in the drug product during stability studies.
06/29/92	Request to Reactivate the IND and New Protocol Amendment: ACS-28. Serial #002 (See Binder 8).
06/29/92	Information Amendment: Toxicology. Serial #003 (See Binder 9).

Exhibit 13

(CLINICAL INVESTIGATION PLAN)

6. SECTION 312.33C CLINICAL INVESTIGATIONAL PLAN

An updated clinical investigational plan is included in Table 6 below.

Table 6: Completed and Ongoing Clinical Studies

Phase	Study No.	Treatment Arms	Evaluation	Duration	N
PHARMACOKINETICS					
2	ACS-32	1. Product with Coe-Pak™ Product Removed at 7 days 2. Product with Octyldent™ Product Not Removed at 7 days 3. Product with No Retentive Material Product Not Removed at 7 days	1. Determine Drug Levels in GCF 2. Assess Product Retention for 28 days	28 days	36
2	ACS-38	1. Product with Coe-Pak™ Product Removed at 7 days 2. Product with Octyldent™ Product Not Removed at 7 days 3. Oral Doxycycline Hyclate	1. Determine Drug Levels in GCF, Serum, & Saliva 2. Assess Product Retention for 90 days in Arm 2	28 days Arms 1 & 3 90 days Arm 2	32
Bioequivalence	AGD9607	1. Product with Octyldent™ Previous Constitution Method 2. Product with Octyldent™ New Constitution Method	1. Determine Drug Levels in GCF	7 days	25
Bioequivalence	AGD9701	1. Product with Octyldent™ 2. Product with no retentive material	1. Determine Drug Levels in GCF	7 days	24
Bioequivalence	AGD9705	1. Product nearing end of shelf life with Octyldent™	1. Determine Drug Levels in GCF	7 days	12
EFFICACY/SAFETY					
2	ACS-28	1. Product with Coe-Pak™ Product Removed at 7 days 2. Placebo with Coe-Pak™ Product Removed at 7 days 3. Alternate Product with Coe-Pak™ Product Removed at 7 days	1. Assess Clinical End Points	9 months	180
	ACS-33	1. Product with Coe-Pak™ Product Removed at 7 days 2. Oral Hygiene	1. Assess Microbial Resistance & Overgrowth	6 months	45
3	ACS-34 ACS-35	1. Product with Coe-Pak™ Product Removed at 7 days 2. Product with Octyldent™ Product Removed at 7 days 3. Oral Hygiene 4. Scaling & Root Planing	1. Assess Clinical End Points	9 months	831 (411 in ACS-34) (420 in ACS-35)
	AGD9603	1. Product with Coe-Pak™ Product Removed at 7 days 2. Product with Octyldent™ Product Not Removed at 7 days 3. Placebo with Octyldent™ Product Not Removed at 7 days	1. Assess Clinical End Points	9 months	605

Exhibit 14

(PROJECT 1010 CORRESPONDENCE INDEX)

ATRIDOX™ Drug Product
(ATRIGEL® Delivery System with Doxycycline Hyclate)
Project 1010
Correspondence Index

Date	Document
08/28/98	Submission to NDA 50-751: Proposed labeling for the ATRIDOX™ Drug Product. See Binder #25.
08/28/98	Letter to Dr. Roy Blay forwarding desk copies of formal submission to the NDA.
09/02/98	Note to File: Phone call from Jake Kelsey, Tony DeCamp and Mary Jane Fornaro, FDA to discuss trade name designation on FPL and Timing of Approval Letter.
09/02/98	Fax from Dr. Roy Blay forwarding Chemistry memoranda re: appropriate nomenclature for ATRIDOX, NDA 50-751.
09/03/98	Note to File: Telecon with FDA Division review to discuss administrative process for approval letter.
09/03/98	Fax/Letter from FDA forwarding **Approval Letter and Labeling for NDA 50-751, ATRIDOX™.**

ATRIDOX™ Drug Product
(ATRIGEL® Delivery System with Doxycycline Hyclate)
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Date	Document
08/06/98	Note to File: Phone conversation with Dr. Blay re: follow up to phone call on 08/03/98.
08/10/98	Letter from FDA to Dr. Gary Bogle enclosing copy of establishment inspection report (EIR) conducted in Redlands, CA on 02/18/98.
08/12/98	Fax to Dr. Roy Blay requesting that he forward the attached letter to Dr. Wilkin re: the completion of the review process of the labeling submission to our NDA.
08/12/98	Note to File: Phone call to Mike Kuchta, FDA Denver District Office, re: final report for ATRIDOX Pre-Approval Inspection.
08/12/98	Note to File: Phone call from Roy Blay re: timing of FDA Internal Review Meeting to finalize labeling for ATRIDOX.
08/13/98	Note to File: Phone call from Roy Blay re: request for update to graphs for ATRIDOX Product Labeling.
08/14/98	Fax to Dr. Roy Blay transmitting updated graphs for ATRIDOX Package Insert.
08/14/98	Note to File: Phone call to Roy Blay re: offer to Dr. Wilkin to respond to letter sent by American Academy of Periodontology (AAP) on July 27, 1998 – AAP letter attached.
08/18/98	Note to File: Phone call to Dr. Roy Blay, to discuss status of label review.
08/18/98	Note to File: Phone call from Jake Kelsey, FDA to John Urheim, Atrix, to discuss letter from AAP.
08/20/98	Note to File: Phone call from Dr. Roy Blay to discuss status of ATRIDOX™ Label Review.
08/21/98	Note to File: Phone call from Roy Blay to discuss status of ATRIDOX™ Label Review.
08/24/98	Fax to Roy Blay re: NDA 50-751 – Safety Update.
08/24/98	Fax from Dr. Roy Blay, FDA, with revised version of the labeling for ATRIDOX™.
08/25/98	Note to File: Phone call to Dr. Roy Blay, re: ATRIDOX™ product labeling review.
08/26/98	Note to File: Phone call to Dr. Roy Blay re: ATRIDOX™ product labeling review.
08/26/98	Fax to Dr. Roy Blay re: NDA 50-751 – Questions on ATRIDOX™ Label.
08/28/98	Note to File: Teleconference with Dr. Jake Kelsey & Dr. Roy Blay re: ATRIDOX™ Product Label – reference Atrix fax dated 08/26/98.

ATRIDOX™ Drug Product
(ATRIGEL® Delivery System with Doxycycline Hyclate)
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Date	Document
07/01/98	Note to File: Phone call to Dr. Roy Blay to discuss reviewer comments on fax correspondence of June 24 and 29, 1998.
07/02/98	Submission to NDA 50-751: ATRIDOX™ Product Labeling Amendment. See Binder #24.
07/06/98	Letter from FDA granting waiver from request sent to FDA 06/26/98.
07/06/98	Note to File: Phone call from Dr. Roy Blay to discuss Dr. Kelsey's response to Dr. Garrett's phone call of July 6, 1998.
07/06/98	Note to File: Phone call to Dr. Roy Blay to request to talk with Jake Kelsey, DDS, FDA Dental Team Leader.
07/07/98	Note to File: Phone call to Dr. Roy Blay to discuss Dr. Kelsey's response to Dr. Garrett's phone call of July 6, 1998.
07/10/98	Note to File: Phone call to Dr. Roy Blay to discuss Dr. Garrett's phone call of July 6, 1998.
07/14/98	Letter from Mary Jean Kozma-Fornaro, FDA/CDER, acknowledging receipt of resubmission to NDA for Controlled Release in Subgingival Application. User fee goal is January 6, 1999. Fax (dated 07/15/98) attached.
07/15/98	Note to File: Dr. Garrett's conversation with Dr. Kelsey.
07/15/98	Note to File: Phone call from Mary Jean Kozma Fornaro, Supervisor Project Management Staff, to discuss classification of resubmission for ATRIDOX NDA.
07/22/98	Fax from Dr. Roy Blay forwarding pharmacokinetics comments on NDA 50-751, agenda itm 3a from Atrix supplement submitted on 07/02/98; requesting further statistical data.
07/23/98	Note to File: Phone call to Dr. Roy Blay to discuss fax correspondence from FDA on 07/22/98 requesting re-analysis of in vitro release data for product constitution comparison and discussion of interactive review process for outstanding labeling issues.
07/24/98	Submission to NDA 50-751: Statistical Re-Analysis of Data Requested by FDA Phamacokinetic Reviewer, Dr. Dan Wang on 07/22/98.
07/27/98	Letter to FDA (Jonathan Wilkin) from Timothy Rose, American Academy of Periodontology re: their "issues" with ATRIDOX labeling.
07/29/98	Note to File: Internet memo to Dr. Kelsey from Dr. Garrett.
08/03/98	Note to File: Phone conversation with Dr. Blay re: Dr. Kelsey's review and if he has any questions.

ATRIDOX™ Drug Product
(ATRIGEL® Delivery System with Doxycycline Hyclate)
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Date	Document
06/04/98	Note to File: Phone call from Dr. Roy Blay re: Atrix request for determination of applicability of ATRIDOX Drug Product to SUPAC semi-solid oral dosage form FDA Guidance – finalized May, 1997 and request to oversticker process validation lots with extended expiration dating period.
06/05/98	Memo to File: Phone call from Dr. Roy Blay re: Atrix request for determination of applicability of ATRIDOX Drug Product to SUPAC Semi-Solid Oral Dosage Form FDA Guidance – finalized May, 1997.
06/11/98	Note to File: Phone call to Dr. Roy Blay re: Dr. DeLap's presence at the meeting and intent on attendees for meeting.
06/12/98	Note to File: Phone call to Sandy Chiles re: logistics for June 17 meeting.
06/12/98	Fax to Sandy Chiles re: efficacy graphs for ATRIDOX Clinical Trials Data.
06/15/98	Note to File: Phone call to Sandy Chiles, FDA Meeting Coordinator, to request overhead projector for June 17 meeting.
06/15/98	Note to File: Phone call to Dr. Roy Blay to request contact after FDA Pre-Meeting regarding ATRIDOX™ Labeling.
06/15/98	Note to File: Phone call to Dr. Roy Blay to request contact after FDA pre-meeting regarding ATRIDOX™ Labeling.
06/16/98	Note to File: Phone call to Dr. Roy Blay to request contact after FDA pre-meeting regarding ATRIDOX™ Labeling.
06/17/98	Note to File: Phone call to Dr. Roy Blay to request contact after FDA pre-meeting regarding ATRIDOX™ Labeling.
06/18/98	Fax from Dr. Blay forwarding letter regarding microbiology discussion.
06/24/98	Fax to Dr. Blay re: points to consider for FDA Post-Meeting.
06/26/98	Letter to Dr. Murray Lumpkin re: Waiver Request for NDA 50-751 for the requirement to submit Form FDA-1639 or FDA Form 3500A for nonserious adverse events.
06/29/98	Fax to Dr. Roy Blay re: Request for Comment: ATRIDOX™ Method of Product Constitution Reference NDA 50-751.
06/29/98	Note to File: Phone call to Dr. Roy Blay to discuss scheduling of teleconferences regarding ATRIDOX™ labeling.
06/30/98	Fax to Dr. Roy Blay re: request for comment on fax correspondence of June 24 and 29 re: NDA 50-751.

ATRIDOX™ Drug Product
(ATRIGEL® Delivery System with Doxycycline Hyclate)
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Date	Document
05/11/98	Note to File: Call from Mary Jean Fornaro, Supervisor, FDA Project Management, re: discussion of submission of Chemistry Information and Teleconference with Dr. Wilkin to discuss labeling materials.
05/11/98	Submission to NDA 50-751: NDA 50-751, ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate). Submission of Meeting Materials for the Requested Product Labeling Meeting June 17, 1998. See. Binder # 23.
05/19/98	Memo to File: Phone call to Roy Blay, Ph.D., FDA Project Manager to request teleconference with Dr. Wilkin regarding labeling meeting materials.
05/27/98	Memo to File: Phone call to Dr. Roy Blay inquiring about the timing of FDA's pre-meeting to review materials forwarded by Atrix.
06/03/98	Memo to File: Phone call to Dr. Roy Blay inquiring about status of request in regards to the Atrix request of May 27, 1998.
06/03/98	Fax to Sandy Chiles forwarding correction page for June 17, 1998 meeting materials.

ATRIDOX™ Drug Product
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Date	Document
04/07/98	Letter from Dr. Roy Blay forwarding the approvable letter and labeling for NDA 50-751.
04/10/98	Fax to Dr. Michael Weintraub re: ATRIDOX; requesting meeting with FDA to discuss issues regarding product labeling for NDA 50-751.
04/10/98	Fax to Dr. Roy Blay transmitting copy of fax sent to Dr. Michael Weintraub requesting meeting with FDA to discuss product labeling for ATRIDOX.
04/10/98	Fax to Dr. Roy Blay re: Atrix intent to file a label amendment to NDA 50-751.
04/10/98	Submission to NDA 50-751: Intent to file an amendment to NDA 50-751 following a meeting to discuss labeling issues with the FDA.
04/21/98	Note to File: ATRIDOX™ Drug Product labeling – Meeting Request calls to Dr. Roy Blay, FDA Project Manager.
04/23/98	Letter from FDA acknowledging receipt of A.Taylor's correspondence dated 03/18/98 that deals with concern FDA had stemming from the evaluation of Atrix nonclinical laboratory facility.
04/23/98	Memo to File: Phone call from Sandy Chiles, FDA Meeting Coordinator to Request Teleconference with Dr. Wilkin and Dr. Kelsey to discuss Atrix meeting request of April 10, 1998.
04/24/98	Memo to File: Phone call to Sandy Chiles, FDA Meeting Coordinator re: scheduling of meeting to discuss ATRIDOX™ Product Labeling Issues.
04/24/98	Submission of amended information for NDA 50-751 re: Update to the NDA new safety information.
04/30/98	Note to File: Phone conversation with Sandy Chiles, CDER re: confirmation of meeting with the FDA and submission of meeting materials for the ATRIDOX™ Drug Product. Meeting Date: **June 17, 1998 at 1:00PM.**
04/30/98	Note to File: Phone conversation with Dr. Roy Blay re: upcoming meeting requested by Atrix, confirmation of same, agenda of meeting and attendees of meeting.
05/07/98	Note to File: Call from Dr. Roy Blay, FDA Project Manager, to discuss request to submit additional stability data.
05/08/98	Submission of Desk Copies for NDA 50-751, ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate). Initial Meeting materials for Product Labeling for ATRIDOX™ Drug Product. See Binder # 22.

ATRIDOX™ Drug Product
(ATRIGEL® Delivery System with Doxycycline Hyclate)
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Date	Document
03/18/98	Note to File: Phone call from Dr. Kelsey, FDA Dental Reviewer & Dr. Roy Blay, FDA Project Manager, to discuss questions on ATRIDOX™ Product Labeling and Comment on update on clinical study requirements for addition of adjunctive label claim for the ATRIDOX™ Product.
03/18/98	Letter(s) to Dr. Roy Blay, FDA Project Manager, C.T. Viswanathan, Ph.D., Associate Director, Office of Compliance; Teena Aiken, Denver District re: Response to outstanding issues regarding the FDA Form 483 received by Atrix on December 2, 1997. See Binder #20.
03/19/98	Fax to Dr. Roy Blay re: response to FDA inquiries for NDA 50-751 – Teleconference of March 18, 1998.
03/19/98	Submission to NDA 50-751: ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) Response to FDA Request for Information. See Binder #21.
03/30/98	Note to File: Call from Dr. Roy Blay forwarding message from Dr. Kelsey re: Atrix can receive final label from FDA either 04/02/98 or 04/03/98.
04/03/98	Fax from Dr. Roy Blay re: Native American Study using the ATRIDOX™ Drug Product.
04/06/98	Fax to Dr. Roy Blay forwarding the revised labeling for NDA 50-751 that has been reviewed by the FDA with their comments/changes.
04/06/98	April 6, 1998 FDA Teleconference Minutes.

ATRIGEL™ Delivery System With Doxycycline Hyclate
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NDA 50-751
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Date	Description
02/25/98	Fax to Dr. Roy Blay re: NDA 50-751: Atrix Response to FDA Proposal for Extended Drug Release Specification as Discussed during Teleconference of February 20, 1998.
02/26/98	Note to File: Call from Mike Kuchta re: setting time to visit Atrix to collect samples of ATRIDOX™ drug product.
02/26/98	Submission of Amended Information to NDA 50-571: Response to Proposed Extended Release Drug Limits and Responses to Clinical Issues. See Binder #18.
02/26/98	Letter to Dr. Blay submitting desk copies of submission of Amended Information to NDA 50-571: Response to Proposed Extended Release Drug Limits and Responses to Clinical Issues.
03/02/98	Submission of Amended Information for NDA 50-751 Submission originally submitted April 7, 1997. See Binder #19.
03/02/98	Letter to Dr. Roy Blay sending desk copies of Submission of Amended Information for NDA 50-751 Submission originally submitted April 7, 1997.
03/03/98	Note to File: Call to Dr. Roy Blay, FDA Project Manager re: Timing of Label Review Meeting within Dental Review Division and Inquire if Dr. Kelsey would like a copy of the response to 483 issued to Dr. Bogle (Atrix Clinical Investigational Site).
03/09/98	Fax to Dr. John Kelsey, FDA Dental Team Leader, re: answers to his inquiries on proposed product labeling for the ATRIDOX™ Drug Product.
03/10/98	Note to File: Call from Dr. Roy Blay re: Question on Proposed Retentive Material for ATRIDOX™ Product.
03/10/98	Note to File: Call to Warren Rumble, FDA DDMAC (301/827-2831) re: Plan for submission of ATRIDOX™ Product Labeling and Promotional Material.

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(03/31/97 -

Date	Description
02/13/98	Note to File: Phone call to Dr. Roy Blay re: status of questions to chemistry reviewers on 02/11/98 and question to statistician on 02/12/98.
02/13/98	Submission to NDA 50-751: ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) Amended information including changes made to the ATRIDOX™ product label since 12/31/97 amendment. See Binder #16.
02/13/98	Desk Copies: enclosing amended label information to Dr. Roy Blay.
02/13/98	Note to File: Phone call from Dr. Roy Blay, FDA Project Manager re: status of Atrix questions for FDA Chemistry & Statistical Reviewer.
02/17/98	Fax to Dr. Roy Blay re: NDA 50-751; Response to FDA Proposal for Extended Release Specification.
02/18/98	Note to File: Phone call from Dr. Roy Blay requesting Electronic Copy of Labeling submitted February 13, 1998.
02/18/98	Submission to NDA 50-751: ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate); amended information of responses to issues discussed with FDA during 02/06/98 teleconference. See Binder #17.
02/18/98	Desk Copies of 02/18/98 amended information sent to Dr. Roy Blay.
02/18/98	Atrix Minutes from February 18, 1998 Teleconference with FDA.
02/20/98	Atrix Minutes from February 20, 1998 Teleconference with FDA.
02/20/98	Fax to Dr. Roy Blay re: NDA 50-751: Atrix & Block Participants for Teleconferences of February 17 and February 20, 1998.
02/24/98	Note to File: Phone call to Dr. Tony DeCamp, FDA Chemistry Team Leader re: request for clarification of discussion from teleconference of February 20, 1998.

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(03/31/97 -

Date	Description
01/29/98	Atrix Minutes of FDA Pre-Approval Inspection Close-Out Meeting for the ATRIDOX™ Drug Product (Reference NDA 50-751).
01/29/98	Note to File: Phone call from Dr. Jose Carrerras, FDA Office of Compliance, requesting information for inspection of clinical investigational sites at Loma Linda (Dr. Bogle), Loma Linda VA (Dr. Kiger), and University of Missouri at Kansas City (Dr. Killoy).
01/29/98	Note to File: Phone call to Dr. John Kelsey, FDA, re: Dr. Garrett's phone call to Dr. Kelsey to inquire as to any possible questions regarding ATRIDOX™ product marketing application, etc.
02/02/98	Letter to Dr. Jose Carrerras submitting information on clinical study sites requested January 29,1998. See Binder #11: University of Missouri, Kansas City - Dr. Killoy See Binder #12: Loma Linda – Dr. Bogle (Vol. 1) See Binder #13: Loma Linda – Dr. Bogle (Vol. 2) See Binder #14: Loma Linda – Dr. Bogle (Vol. 3) See Binder #15: Loma Linda, VA – Dr. Kiger
02/06/98	Fax to Dr. Blay re: Chemistry Teleconference of February 6, 1998 – Requested by FDA with reference to NDA 50-751.
02/07/98	Notes from 02/06/98 teleconference with FDA.
02/11/98	Fax to Dr. Blay with clarifications of the Statistical Request from the FDA.
02/11/98	Note to File: Phone call to Dr. Roy Blay, FDA Project Manager re: Question to Chemistry Reviewers" What is Rationale for 75% Lower Specification Limit for 24 hour Assay Time Point?
02/11/98	Note to File: Phone call from Dr. Roy Blay re: Request for Biostatistical Test on ACS-32 Study.

ATRIGEL™ Delivery System With Doxycycline Hyclate
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NDA 50-751
(03/31/97 -

Date	Description
01/12/98	Note to File: Phone call to Dr. John Kelsey, FDA Dental Reviewer re: response to Dr. Kelsey's request to clarify duplicated subject numbers in ACS-34 & 35.
01/15/98	Note to File: Phone call to Mike Kuchta requesting time when he would be able to complete the pre-approval inspection of Atrix.
01/21/98	Note to File: Phone call to Dr. Roy Blay, re: how many copies of layout for product label should be submitted to FDA? And, further inquiries about labeling.
01/22/98	Note to File: Phone call from Dr. Roy Blay requesting an electronic copy of SAS Format Library for AGD9603 clinical study.
01/26/98	Submission to FDA: NDA 50-751, ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) enclosing 2 copies of diskette containing SAS Format Catalogue for Clinical Study AGD9603, hard copy of program. See Binder #10.
01/26/98	Desk Copy of diskette containing SAS Format Catalogue for Clinical Study AGD9603, also enclosing 2 copies of diskette – 1/Statistical; 1/Archive.
01/26/98	Note to File: Phone call from Mike Kuchta, FDA Denver District Office, re: return for completion of pre-approval inspection: January 27, 28, 29, 1998.
01/27/98	Note to File: Phone call to Dr. Roy Blay, re: Dr. Garrett's schedule of courtesy call to Dr. Kelsey.
01/27/98	Note to File: Phone call from Cody Riley, Atrix to Mike Kuchta re: manufacturing of bulk ATRIGEL® had been postponed until January 29, 1998.
01/28/98	Note to File: Call from Mike Kuchta, FDA Denver, re: his return to Atrix would be January 28 and 29, 1998.

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NDA 50-751
(03/31/97 -

Date	Description
12/05/97	Phone call from Dr. Roy Blay, FDA Project Manager, 301/827-2023, and FDA Chemistry Reviewers, Dr. Ernie Pappas and Dr. Wilson DeCamp to discuss fax correspondence of December 3 from Atrix requesting clarification of Item #9 in FDA's letter of November 26, 1997 re: fax correspondence from Atrix of December 3, 1997.
12/15/97	Letter/Response to Dr. Roy Blay/Teena Aiken (Denver District) – NDA 50-751. Response to Form FDA 483/GLP audit received on 12/02/97. See Binder #7.
12/29/97	Note to File: Phone call to Mike Kuchta, FDA Denver District Investigator re: update on status of equipment validation for ATRIDOX product.
12/31/97	Submission of NDA 50-751 Amendment – Clinical Section. See Binder #8.
12/31/97	Table of Contents for shipment of boxes to FDA – Amendment (Clinical) Submission
01/06/98	Submission of NDA 50-751 Amendment – Chemistry Information. See Binder #9.
01/08/98	Letter to Dr. Roy Blay enclosing diskette containing ATRIDOX drug product Package Insert information.
01/08/98	Note to File: Phone call to Mike Kuchta indicating Atrix would have all outstanding items of the Pre-Approval Inspection completed by January 16, 1998.
01/08/98	Letter to Gary Dean of Denver District Office submitting Field Copy of Amended Chemistry Information that was submitted to FDA.
01/09/98	Memo re: Elaine Gazdeck's phone conversation with Dr. Kelsey and his request that we clarify the patient number for a patient in ACS-34 & 35, patient's appear in 12/31/97 Amendment, Vol. 4, pages 219, 220 & 221.

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Date	Description
12/05/97	Phone call from Dr. Roy Blay, FDA Project Manager, 301/827-2023, and FDA Chemistry Reviewers, Dr. Ernie Pappas and Dr. Wilson DeCamp to discuss fax correspondence of December 3 from Atrix requesting clarification of Item #9 in FDA's letter of November 26, 1997 re: fax correspondence from Atrix of December 3, 1997.
12/15/97	Letter/Response to Dr. Roy Blay/Teena Aiken (Denver District) – NDA 50-751. Response to Form FDA 483/GLP audit received on 12/02/97. See Binder #7.
12/29/97	Note to File: Phone call to Mike Kuchta, FDA Denver District Investigator re: update on status of equipment validation for ATRIDOX product.
12/31/97	Submission of NDA 50-751 Amendment – Clinical Section. See Binder #8.
12/31/97	Table of Contents for shipment of boxes to FDA – Amendment (Clinical) Submission
01/06/98	Submission of NDA 50-751 Amendment – Chemistry Information. See Binder #9.
01/08/98	Letter to Dr. Roy Blay enclosing diskette containing ATRIDOX drug product Package Insert information.
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Date	Description
11/20/97	Note to File: Phone call from Michael Kuchta, FDA Denver District Office, re: further scheduling of Pre-Approval Inspection for NDA 50-751 and discussion of conversation with CDER Chemistry Reviewers.
11/21/97	Note to File: Phone call to Michael Kuchta, FDA Denver District Office, re: requirements for equipment validation – NDA 50-751.
11/21/97	Fax to Dr. Roy Blay re: confirmation of answers given during teleconference with Chemistry Reviewers to discuss changes for secondary packaging for ATRIDOX™ Drug Product conducted 11/20/97 – Reference NDA 50-751.
11/22/97	Fax to Dr. Roy Blay re: categorical exemption for environmental assessment – NDA 50-751.
11/25/97	Letter to Dr. Roy Blay re: requested desk copies (Volumes 1-4 and 6-8) of NDA 50-751.
11/26/97	Letter from FDA re: additional questions from CMC reviewers.
12/01/97	Submission to FDA re: amended chemistry and statistical review information for NDA 50-751. See Binder #5.
12/01/97	Submission of addition information requested by Dr. Ernie Pappas (i.e., Analytical Method, Method Validation, Stability Protocol, Analysis Data) – Desk Copy for Dr. Blay's reference. See Binder #6.
12/03/97	Memo to File: Phone call from Dr. Roy Blay, FDA Project Manager – 301/827-2023 and FDA Chemistry Reviewers Dr. Ernie Pappas and Dr. Wilson DeCamp to Discuss Letter from FDA of November 26, 1997 with questions on CMC Technical Section of NDA 50-751.
12/03/97	Fax to Dr. Roy Blay Re: Request for clarification of item #9 from FDA Letter of 11/26/97. Reference NDA 50-751.
12/05/97	Phone call to Dr. Roy Blay, FDA Project Manager, regarding fax correspondence from Atrix of December 3, 1997.

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Date	Description
10/23/97	Letter to Dr. Roy Blay re: NDA 50-751; Desk Copy, Statistical Information.
10/23/97	Fax to Dr. Roy Blay re: timing of amendments for NDA 50-751.
10/27/97	Phone call from Dr. John Kelsey, FDA Dental Reviewer, 301/827-2035, per request from Atrix for conversation re: timing of Clinical Amendments for NDA 50-751.
11/05/97	Letter to Dr. Jose Carrerras re: requested ACS-34 &35 Study information. See Binder #4.
11/14/97	Note to File: Phone call from Dr. Ernie Pappas, FDA Chemistry Reviewer, and Dr. Roy Blay, FDA Project Manager (301/827-2023), re: container/closure information for NDA 50-751.
11/14/97	Note to File: Call from Mike Kuchta (303/236-3059) re: discussion with Dr. Tony DeCamp and Dr. Ernie Pappas on behalf of Atrix; relaying information on status of equipment for commercial manufacturing process of ATRIDOX™ product.
11/17/97	Note to File: Call from Mike Kuchta re: continuation of Pre-Approval Inspection for ATRIDOX™ Product.
11/18/97	Note to File: Phone call from Dr. Roy Blay, FDA Project Manager, requesting desk copy of Volumes 1-4 of NDA 50-751.
11/18/97	Fax to Dr. Roy Blay re: request for teleconference with Chemistry Reviewer to discuss changes for secondary packaging for ATRIDOX™ Drug Product – Reference NDA 50-751.
11/18/97	Note to File: Phone call from Dr. Roy Blay re: reference to EIAR in the NDA and 06/29/97 Federal Register Notice.

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Date	Description
06/24/97	Phone call to Dr. Hal Blatt, CSO, to determine status of reply to letter of May 12, 1997 to Dr. Wilken concerning clinical study policies.
06/25/97	Fax from Dr. Hal Blatt, CSO, FDA, re: FDA Meeting minutes on NDA 50-751 on 05/20/97.
06/27/97	Phone call to Dr. John Kelsey, FDA Dental Reviewer (301/827-2035) re: response to clinical study design proposal for Adjunctive Claim (Atrix Clinical Study AGD9609).
06/30/97	Letter to Dr. Hal Blatt, CSO, FDA re: submitting desk copies, reference articles from Volume 9, Articles 1-61 from Section 5.10.3. See Binder #4.
07/11/97	Phone call to Dr. John Kelsey, FDA Dental Reviewer (301/827-2035) from Dr. Steve Garrett re: AGD9609 Clinical Study Proposal.
07/16/97	Telephone call from CMC reviewer to discuss review of CMC data.
07/21/97	NDA 50-751; Requested information from CMC Teleconference of July 16, 1997.
07/21/97	Fax from Dr. Hal Blatt, CSO re: forwarding comments from Clinical reviewer on Submission #078 on IND34690.
07/29/97	Fax from Dr. Hal Blatt, CSO re: request to send Desk Copy of Disk with Study Report on ACS-38 in WordPerfect 6.1.
07/30/97	NDA 50-751; Requested information from fax correspondence of July 29, 1997 – forwarding disk to Dr. Hal Blatt, CSO.
10/22/97	Phone call to Dr. Jose Carrerras, FDA Office of Compliance, 301-594-1032: Request for Information from NDA 50-751.
10/23/97	Memo to file re: Phone call from Dr. Roy Blay (301/827-2023) to Elaine Gazdeck requesting statistical information from NDA 50-751.

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Date	Description
05/21/97	Breakfast Meeting with Dr. Kelsy, Dr. Hyman & Dr. Srinivasan, FDA Reviewers.
05/23/97	Fax to Dr. Hal Blatt, CSO re: letter to Dr. Kelsey re: his inquiry about evaluation of safety data on ATRIDOX™.
05/23/97	Submission NDA 50-751: ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) submitting Desk Copies of reference articles from Volume 9; Articles 1-61 from Section 5.10.3. See binder #3.
05/28/97	Phone call from Dr. Hal Blatt, CSO re: his concerns of the reference articles that were forwarded to his attention for the Pharm/Tox reviewer that they were not officially submitted to the NDA.
05/29/97	Phone call to Mike Roosevelt in FDA Financial Office (301/827-5088, Fax: 301/443-8581).
05/29/97	Fax to Michael Roosevelt, FDA, Division of Accounting, re: requested information for electronic reimbursement of User Fee.
06/06/97	Submission of NDA 50-751: ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) submitting Atrix response to FDA meeting minutes from the Pre-NDA meeting (01/07/97), memo re: Dr. Garrett's discussion with Drs. Kelsey, Hyman & Srinivasan.
06/06/97	Fax to Dr. Hal Blatt, CSO re: request for response from FDA regarding AGD9609 Study Design.
06/06/97	Phone conversation with Dr. Hal Blatt, FDA CSO re: acceptance of NDA 50-751 for filing.
06/06/97	Phone conversation with Dr. Hal Blatt, FDA CSO re: response to clinical study design proposal for adjunctive claim (Atrix Clinical Study AGD9609) and request for clarification on FDA Meeting Minutes.

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Date	Description
05/07/97	Fax from Dr. Hal Blatt, CSO re: PK reviewer's responses to Atrix fax dated 05/06/97.
05/07/97	Phone call to Kathleen Locke in the Office of the Commissioner at FDA (301/827-3390) re: date of NDA 50-751 Submission.
05/07/97	Phone call from FDA Biostatistical Reviewers Dr. R.Srinivasan & Dr. Ping Gao (Robin Anderson was the Coordinating CSO for Dr. Hal Blatt) to Susan Duke, Atrix Biostatistician.
05/12/97	Phone call to Dr. Ernie Pappas, FDA, Chemistry Reviewer, re: response faxed to Pappas re: Ranbaxy.
05/12/97	Phone call from Dr. Hal Blatt, CSO, FDA re: Establishment Registration Number or Central File Number for Ranbaxy.
05/12/97	Letter to Dr. Jonathan K. Wilken re: policy on clinical study design for periodontal drug products.
05/14/97	Phone calls from Dr. Hal Blatt, CSO, FDA re: request for responses to the 4 month safety update for NDA 50-751 and the proposed clinical study AGD9609 that was submitted to IND 34690.
05/14/97	Phone call from Dr. Ernie Pappas and Dr. Tony DeCamp re: preapproval inspection questions.
05/20/97	Submission NDA 50-751; ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) submitting amended Pharmacokinetic, Chemistry & Biostatistical Review. See Binder #2.
05/21/97	Submission NDA 50-751; ATRIDOX™ (ATRIGEL® Delivery System with Doxycycline Hyclate) submitting Desk copies of amended Pharmacokinetic, Chemistry & Biostatistical Review to Dr. Hal Blatt, CSO, Pharmacokinetic Review & Statistical Reviewer.
05/21/97	Fax from Dr. Hal Blatt, CSO & Clinical Reviewer re: safety update proposal.

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Date	Description
04/25/97	Letter to Dr. Hal Blatt, CSO enclosing desk copies of two submission forwarded to FDA in the last 10 days. (#1: NDA 50-751 submitted 04/17/97 and IND 34690 submitted 04/24/97.)
04/25/97	Letter from FDA re: Prescription Drug User Fee Act of 1992; Small Business Exception Request. FDA File No. 97.046.
04/29/97	Letter from FDA re: confirmation of receipt of NDA and User Fee.
04/30/97	Telephone call from Dr. Hal Blatt, CSO re: questions about 45-day review check list for NDA.
04/30/97	Responses to Dr. Hal Blatt's questions re: 45-day review check list.
05/01/97	Fax from FDA re: deferral letter for ATRIDOX™.
05/02/97	Telephone call from Dr. Tony DeCamp, FDA Chemistry Team Leader.
05/05/97	Telephone call from Dr. Hal Blatt, CSO re: request copies for pharmacologist of reference articles.
05/05/97	NDA 50-751; Desk Copies, Reference Articles from Volume 9, Articles 1-61 from Section 5.10.3.
05/06/97	Phone call to Dr. Hal Blatt, FDA CSO re: his request for response to proposal for 4 month safety update and proposed clinical study design.
05/06/97	Fax from Dr. Hal Blatt, CSO re: questions on PK and Biostats.
05/07/97	Fax to Dr. Hal Blatt, CSO re: requested information from PK reviewer and memo to file of voice mail left for Dr. Blatt informing of incoming fax.
05/07/97	Fax to Dr. Hal Blatt, CSO re: reuqested information from Chemistry reviewer re: Establishment Registration Numbers for Ranbaxy & Atrix and memo to file of voice mail left for Dr. Blatt informing of incoming fax.

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Date	Description
03/28/97	Request for User Fee Reduction based on small business exception. Letter to Chief Mediator & Ombudsman Officer.
03/31/97	Letter to FDA (Dr. Hal Blatt, CSO) submitting NDA 50-751.
03/31/97	Letter to FDA, Denver District Office (Gary Dean, Director) submitting field copy of NDA 50-751.
04/02/97	Letter to Mellon Bank transferring User Fee for NDA 50-751 submitted 03/31/97.
04/02/97	Fax to Dr. Hal Blatt, CSO informing him of confirmation that Atrix has paid the user fee for NDA 50-751.
04/02/97	Letter from FDA re: Prescription Drug User Fee Act of 1992; Small Business Exception Request. File #97.046.
04/04/97	Letter to Dr. Hal Blatt, CSO re: electronic copies of information submitted in NDA 50-751.
04/10/97	Letter from FDA to Small Business Administration re: request for size determination. FDA File No. 97.046.
04/14/97	Information requests for NDA 50-751 from Dr. Hal Blatt, FDA CSO.
04/16/97	Submission NDA 50-751: ATRIDOX™ (ATRIGEL® Devliery System with Doxycycline Hyclate) submitting amended patent information, debarment certification and User Fee cover sheet for NDA 50-751. See Binder #1.
04/16/97	NDA 50-751: Desk Copies, Volume 1. Electronic Copy of Clinical/Statistical Technical Section.
04/17/97	NDA 50-751. ATRIGEL® Delivery System with Doxycycline Hyclate. Request for response to proposal for safety amendment.